Precocious Puberty

Precocious puberty is defined as early activation of the hypothalamic-pituitary-gonadal axis, resulting in the development of secondary sexual characteristics and fertility.[22,23] Classically, sexual development was considered precocious and warranting investigation when it occurred before 8 years of age for girls and before 9 years of age for boys. However, these criteria were revised based on an office pediatric study of more than 17,000 American girls.[24] Precocious puberty is now defined as the appearance of secondary sexual development before the age of 7 years in white girls and 6 years in African American girls.[23] In boys of both races, the lower age limit remains 9 years; however, it is recognized that puberty can develop earlier in boys with obesity (an increasingly common problem).[23] Precocious sexual development may be idiopathic or may be caused by gonadal, adrenal, or hypothalamic disorders. Benign and malignant tumors of the central nervous system (CNS) can cause precocious puberty. These tumors are thought to remove the inhibitory influences normally exerted on the hypothalamus during childhood. Central nervous system tumors are found more often in boys with precocious puberty than in girls. In girls, most cases are idiopathic.

Diagnosis of precocious puberty in girls is based on physical findings of early thelarche (i.e., beginning of breast development), adrenarche (i.e., beginning of augmented adrenal androgen production), and menarche (i.e., beginning of menstrual function) in girls. The most common sign in boys is early genital enlargement. Radiologic findings may indicate advanced bone age. Persons with precocious puberty usually are tall for their age as children but short as adults because of the early closure of the epiphyses. MRI or CT should be used to exclude intracranial lesions.

Depending on the cause of precocious puberty, the treatment may involve surgery, medication, or no treatment. The administration of a long-acting GnRH agonist results in a decrease in pituitary responsiveness to GnRH, leading to decreased secretion of gonadotropic hormones and sex steroids (i.e., due to down-regulation of GnRH receptors). Parents often need education, support, and anticipatory guidance in dealing with their feelings and the child's physical needs and in relating to a child who appears older than his or her years.

SUMMARY CONCEPTS

- With the exception of growth hormone (GH), the hypothalamus and anterior pituitary gland form a unit that controls the function of the thyroid gland, adrenal cortex, ovaries, and testes.
- Disorders of the anterior pituitary are uncommon but may present with a variety of manifestations including hormone hyper- or hyposecretion and/or localized mass effects that cause compression of the optic chiasm or basal portion of the brain.
- Growth hormone, which is produced by somatotropes in the anterior pituitary, is necessary for linear bone growth in children, as well as affecting the rate at which cells transport amino acids across their cell membranes and the rate at which they utilize carbohydrates and fatty acids. The effects of GH on linear growth require insulin-like growth factors (IGFs), which are produced mainly by the liver.
- In children a GH (or IGF) deficiency interferes with linear bone growth, resulting in short stature or dwarfism, and an excess results in increased linear growth or gigantism. In adults, GH deficiency represents a deficiency carried over from childhood or one that develops during adulthood as the result of a pituitary tumor or its treatment; and a GH excess in adults results in acromegaly, which involves overgrowth of the cartilaginous parts of the skeleton, enlargement of the heart and other organs, and metabolic disturbances in fat and carbohydrate metabolism.
- Alterations in childhood growth include short or tall stature. Short stature can occur as a variant of normal growth, idiopathic short stature, or as the result of endocrine disorders, chronic illness, malnutrition, emotional disturbances, chromosomal disorders, or GH deficiency. Tall stature can occur as a variant of normal growth (i.e., genetic tall stature or constitutional tall stature) or as the result of a chromosomal abnormality or GH excess.
- Precocious puberty defines a condition of early activation of the hypothalamic-pituitary-gonadal axis (i.e., before 6 years of age in African American girls and 7 years of age in white girls, and before 9 years of age in boys of both races), resulting in the development of secondary sexual characteristics and fertility. It causes tall stature during childhood but results in short stature in adulthood because of the early closure of the epiphyses.

Thyroid Hormone Disorders

The thyroid gland, which is the body's largest single organ specialized for hormone production, plays a major role in the processes of almost all body cells.

Structure and Function of the Thyroid Gland

The thyroid gland is a shield-shaped structure located immediately below the larynx in the anterior middle portion of the neck[25,26] (Fig. 32-5A). It is composed of

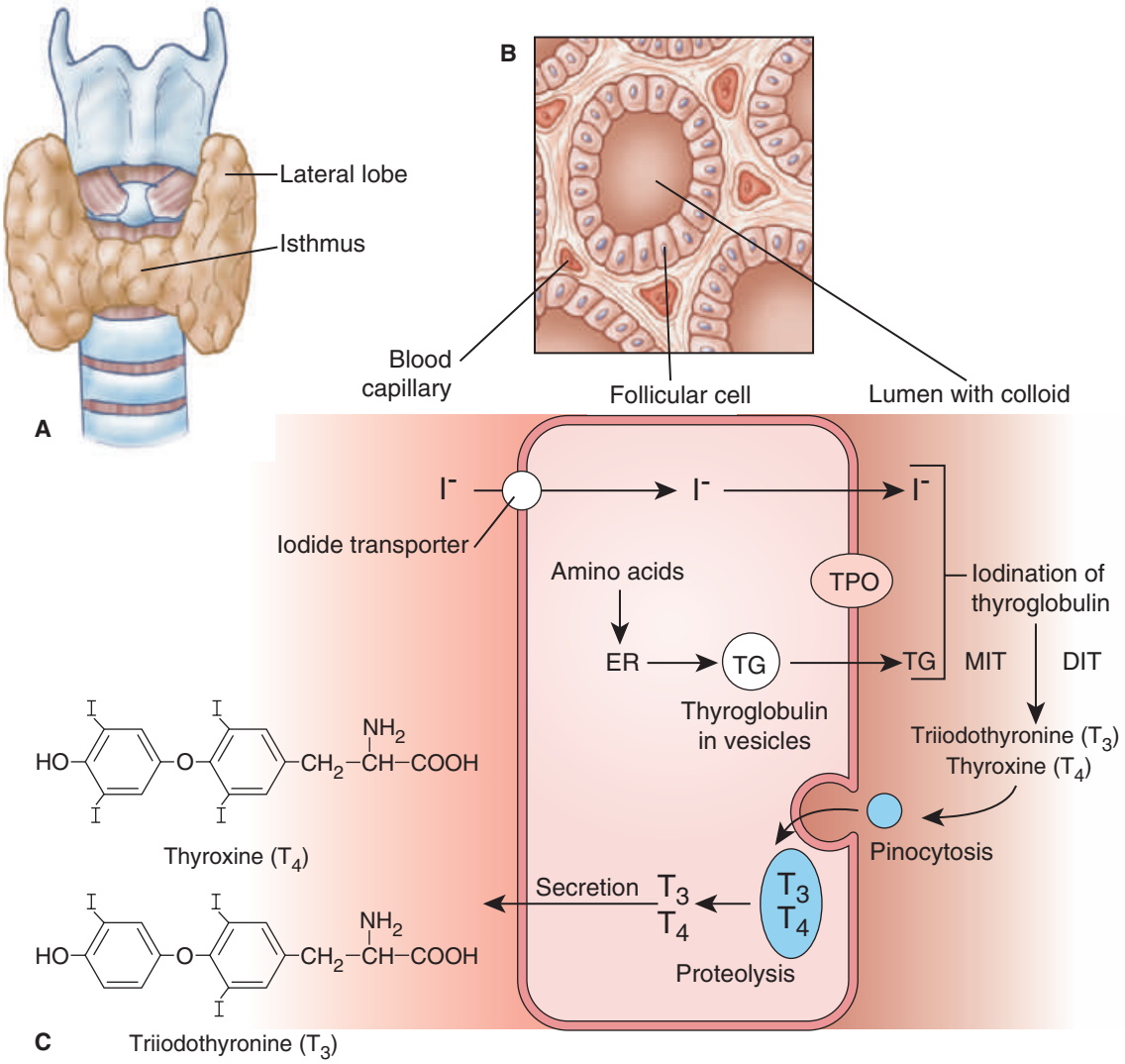

FIGURE 32-5. **(A)** The thyroid gland. **(B)** Microscopic structure of thyroid follicles. **(C)** Cellular mechanisms for transport of iodide (I^-), oxidation of I^- by thyroperoxidase (TPO), coupling of oxidized I^- with thyroglobulin (TG) to form thyroid hormones, and movement of T_3 and T_4 into the follicular cell by pinocytosis and release into the blood. ER, endoplasmic reticulum; MIT, monoiodotyrosine; DIT, diiodotyrosine.

a large number of tiny, saclike structures called *follicles* (Fig. 32-5B). These are the functional units of the thyroid. Each follicle is formed by a single layer of epithelial (follicular) cells and is filled with a secretory substance called *colloid*, which consists largely of a glycoprotein–tyrosine complex called *thyroglobulin* that contains 140 tyrosine amino acids. In the process of thyroid hormone synthesis, iodide is attached to these tyrosine molecules. Both thyroglobulin and iodide are secreted into the colloid of the follicle by the follicular cells.

The thyroid is remarkably efficient in its use of iodide. A daily absorption of 150 to 200 µg of dietary iodide is sufficient to form normal quantities of thyroid hormone. In the process of removing it from the blood and storing it for future use, iodide (I^-) is pumped into the follicular cells against a concentration gradient by an intrinsic membrane protein called the *Na^+/I symporter* (NIS).[25] At the apical border, a second transport protein called *pendrin* moves iodide into the colloid, where it is involved in hormone production. The NIS is stimulated by both TSH and the TSH receptor–stimulating antibody found in Graves' disease (to be discussed). Mutations in the pendrin gene (*PDS*) have been found in persons with goiter and congenital deafness (Pendred syndrome).

Synthesis of Thyroid Hormones

Once inside the follicle, most of the iodide is oxidized by the enzyme thyroid peroxidase (TPO) in a reaction that facilitates combination with a tyrosine molecule to form monoiodotyrosine (MIT), and a second iodide is then attached to make diiodotyrosine (DIT). Two diiodotyrosine molecules are coupled to form thyroxine (T_4), or a monoiodotyrosine and a diiodotyrosine are coupled to form triiodothyronine (T_3). Only T_4 (90%) and T_3 (10%) are released into the circulation (Fig. 32-5C).

There is evidence that T_3 is the active form of the hormone and that T_4 is converted to T_3 before it can act physiologically.

Thyroid hormones are bound to thyroxine-binding globulin (TBG) and other plasma proteins, mainly transthyretin and albumin, for transport in the blood. Only the free hormone enters cells and regulates the pituitary feedback mechanism. Protein-bound thyroid hormone forms a large reservoir that is slowly drawn on as free thyroid hormone is needed. More than 99% of T_4 and T_3 is carried in the bound form.[25,26] TBG carries approximately 75% of T_4 and T_3, transthyretin binds approximately 10% of circulating T_4 and lesser amounts of T_3, and albumin binds approximately 15% of circulating T_4 and T_3.

A number of conditions and pharmacologic agents can decrease the amount of binding protein in the plasma or influence hormone binding. Congenital TBG deficiency is an X-linked trait that occurs in 1 of every 5000 live births. Glucocorticoid medications and systemic disease conditions such as protein malnutrition, nephrotic syndrome, and cirrhosis decrease TBG concentrations. Medications such as phenytoin, salicylates, and diazepam can affect the binding of thyroid hormone to normal concentrations of binding proteins.

Regulation of Thyroid Hormone Secretion

The secretion of thyroid hormone is regulated by the hypothalamic-pituitary-thyroid feedback system (Fig. 32-6). In this system, thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus, increases the release of TSH from the anterior pituitary gland. Thyroid stimulating hormone, in turn, binds to the TSH receptor on thyroid epithelial cells stimulating essentially every aspect of thyroid function, including promoting the release of thyroid hormones from the thyroid follicles into the bloodstream, and increasing the activity of the iodide pump and iodination of tyrosine to increase production of the thyroid hormones. Thyroid stimulating hormone also has a strong tropic effect, stimulating hypertrophy, hyperplasia, and survival of thyroid epithelial cells.

Increased levels of thyroid hormone act in the feedback inhibition of TRH or TSH. High levels of iodide (e.g., from iodide-containing cough syrup or kelp tablets) also cause a temporary decrease in thyroid activity that lasts for several weeks, probably through a direct inhibition of TSH on the thyroid. Cold exposure is one of the strongest stimuli for increased thyroid hormone production and probably is mediated through TRH from the hypothalamus. Various emotional reactions also can affect the output of TRH and TSH and therefore indirectly affect secretion of thyroid hormones.

Actions of Thyroid Hormone

Most of the major organs in the body are affected by altered levels of thyroid hormone. Thyroid hormone increases metabolism and protein synthesis; it is necessary for growth and development in children, including mental development and attainment of sexual maturity; and it affects the function of many other organ systems in the body. These actions are mainly mediated by T_3.

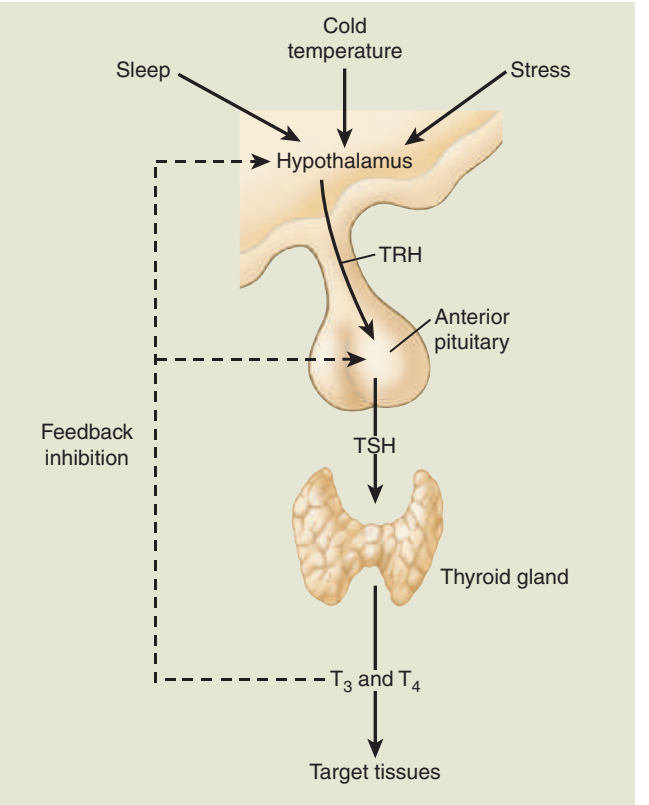

FIGURE 32-6. The hypothalamic-pituitary-thyroid feedback system, which regulates the body levels of thyroid hormone. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

In the cell, T_3 binds to a nuclear receptor, resulting in transcription of specific thyroid hormone response genes.[25,26]

Metabolic Rate. Thyroid hormone increases the metabolism of all body tissues except the retinas, spleen, testes, and lungs. The basal metabolic rate can increase to 60% to 100% above normal when large amounts of T_4 are present. As a result of this higher metabolism, the rate of glucose, fat, and protein use increases. Lipids are mobilized from adipose tissue, and the catabolism of cholesterol by the liver is increased. Blood levels of cholesterol are decreased in hyperthyroidism and increased in hypothyroidism. Muscle proteins are broken down and used as fuel, probably accounting for some of the muscle fatigue that occurs with hyperthyroidism. The absorption of glucose from the gastrointestinal tract is increased. Because vitamins are essential parts of metabolic enzymes and coenzymes, an increase in metabolic rate tends to accelerate the use of vitamins and cause vitamin deficiency.

Cardiorespiratory Function. Cardiovascular and respiratory functions are strongly affected by thyroid function. With an increase in metabolism, there is a rise in oxygen consumption and production of metabolic end products, with an accompanying increase in vasodilation. Blood flow to the skin, in particular, is augmented as a means of dissipating the body heat that

results from the higher metabolic rate. Blood volume, cardiac output, and ventilation are increased as a means of maintaining blood flow and oxygen delivery to body tissues. Heart rate and cardiac contractility are increased as a means of maintaining the needed cardiac output, whereas there is little change in blood pressure because the increase in vasodilation tends to offset the increase in cardiac output.

Gastrointestinal Function. Thyroid hormone enhances gastrointestinal function, causing an increase in motility and production of gastrointestinal secretions that often results in diarrhea. An increase in appetite and food intake accompanies the higher metabolic rate that occurs with increased thyroid hormone levels. At the same time, weight loss occurs because of the increased use of calories.

Neuromuscular Effects. Thyroid hormone has marked effects on neural control of muscle function and tone. Slight elevations in hormone levels cause skeletal muscles to react more vigorously, and a drop in hormone levels causes muscles to react more sluggishly. In the hyperthyroid state, a fine muscle tremor is present. The cause of this tremor is unknown, but it may represent an increased sensitivity of the neural synapses in the spinal cord that control muscle tone. In the infant, thyroid hormone is necessary for normal brain development. The hormone enhances cerebration; in the hyperthyroid state, it causes extreme nervousness, anxiety, and difficulty in sleeping.

Evidence suggests a strong interaction between thyroid hormone and the sympathetic nervous system. Many of the signs and symptoms of hyperthyroidism suggest overactivity of the sympathetic division of the autonomic nervous system, such as tachycardia, palpitations, and sweating. Tremor, restlessness, anxiety, and diarrhea also may reflect autonomic nervous system imbalances. Drugs that block sympathetic activity have proved to be valuable adjuncts in the treatment of hyperthyroidism because of their ability to relieve some of these undesirable symptoms.

Tests of Thyroid Function

Various tests aid in the diagnosis of thyroid disorders.[25,27] Measures of T_3, T_4, and TSH have been made available through immunoassay methods. The free T_4 test measures the unbound portion of T_4 that is free to enter cells to produce its effects. TSH levels are used to differentiate between primary and secondary thyroid disorders. T_3, T_4, and free T_4 levels are low in primary hypothyroidism, and the TSH level is elevated. The assessment of thyroid autoantibodies (e.g., anti-TPO antibodies in Hashimoto thyroiditis) is important in the diagnostic workup and consequent follow-up of patients with thyroid disorders.

The radioiodine (^{123}I) uptake test measures the ability of the thyroid gland to remove and concentrate iodine from the blood. Thyroid scans (^{123}I, ^{99m}Tc-pertechnetate) can be used to detect thyroid nodules and determine the functional activity of the thyroid gland. Ultrasonography can be used to differentiate cystic from solid thyroid lesions, and CT and MRI scans are used to demonstrate tracheal compression or impingement on other neighboring structures. Fine needle aspiration biopsy of a thyroid nodule has proved to be the best method for differentiation of benign from malignant thyroid disease.

Thyroid Disorders

An alteration in thyroid function can present as a hypofunctional or a hyperfunctional state. The manifestations of these two altered states are summarized in Table 32-1. Disorders of the thyroid may be due to a

TABLE 32-1 Manifestations of Hypothyroid and Hyperthyroid States

Level of Organization	Hypothyroidism	Hyperthyroidism
Basal metabolic rate	Decreased	Increased
Sensitivity to catecholamines	Decreased	Increased
General features	Myxedematous features	Exophthalmos (in Graves' disease)
	Deep voice	Lid lag
	Impaired growth (child)	Accelerated growth (child)
Blood cholesterol levels	Increased	Decreased
General behavior	Mental retardation (infant)	Restlessness, irritability, anxiety
	Mental and physical sluggishness	Hyperkinesis
	Somnolence	Wakefulness
Cardiovascular function	Decreased cardiac output	Increased cardiac output
	Bradycardia	Tachycardia and palpitations
Gastrointestinal function	Constipation	Diarrhea
	Decreased appetite	Increased appetite
Respiratory function	Hypoventilation	Dyspnea
Muscle tone and reflexes	Decreased	Increased, with tremor and twitching
Temperature tolerance	Cold intolerance	Heat intolerance
Skin and hair	Decreased sweating	Increased sweating
	Coarse and dry skin and hair	Thin and silky skin and hair
Weight	Gain	Loss

congenital defect in thyroid development, or they may develop later in life, with a gradual or sudden onset.

Goiter is an increase in the size of the thyroid gland. It can occur in hypothyroid, euthyroid, and hyperthyroid states. Goiters may be toxic, producing signs of extreme hyperthyroidism or thyrotoxicosis, or they may be nontoxic. Goiters may be diffuse, involving the entire gland without evidence of nodularity, or they may contain nodules. Diffuse goiters usually become nodular.

Diffuse nontoxic and multinodular goiters are the result of compensatory hypertrophy and hyperplasia of follicular epithelium from some derangement that impairs thyroid hormone output. The degree of thyroid enlargement usually is proportional to the extent and duration of thyroid deficiency. Multinodular goiters produce the largest thyroid enlargements (Fig. 32-7). When sufficiently enlarged, they may compress the esophagus and trachea, causing difficulty in swallowing, a choking sensation, and inspiratory stridor. Such lesions also may compress the superior vena cava, producing distention of the veins of the neck and upper extremities, edema of the eyelids and conjunctiva, and syncope with coughing.

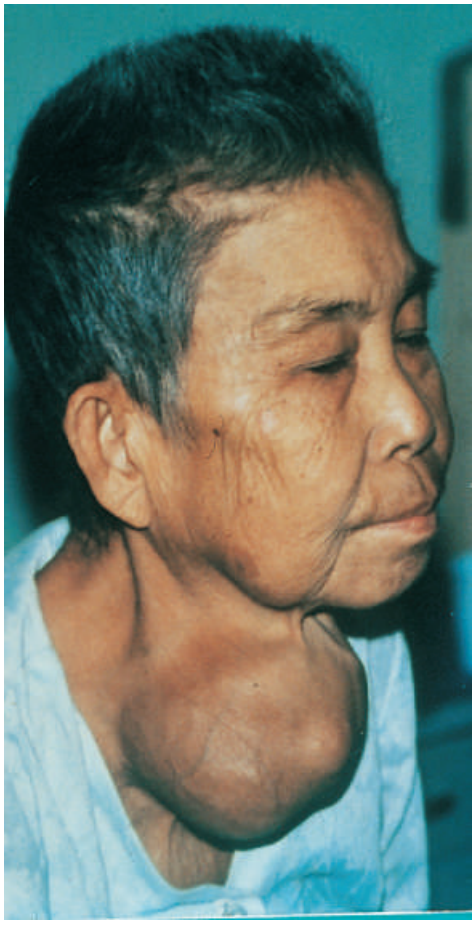

FIGURE 32-7. Nontoxic goiter in a middle aged woman. The thyroid has enlarged to produce a conspicuous neck mass. (From: Merino MJ, Quezado M. The endocrine system. In: Rubin R, Strayer DS, eds. *Rubin's Pathology: Clinicopathologic Foundations of Medicine*, 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012:1047.)

Hypothyroidism

Hypothyroidism can occur as a congenital or an acquired defect. Congenital hypothyroidism develops prenatally and is present at birth. Acquired hypothyroidism develops later in life because of primary disease of the thyroid gland or secondary to disorders of hypothalamic or pituitary origin.

Congenital Hypothyroidism. Thyroid hormone is essential for normal growth and brain development, almost half of which occurs during the first 6 months of life.[25] Hypothyroidism in an infant may result from a congenital lack of the thyroid gland or from abnormal biosynthesis of thyroid hormone or deficient TSH secretion.[25] If untreated, congenital hypothyroidism causes mental retardation and impairs physical growth.

With congenital lack of the thyroid gland, the infant usually appears normal and functions normally at birth because of hormones supplied in utero by the mother. Prolongation of physiologic jaundice, caused by delayed maturation of the hepatic system for conjugating bilirubin, may be the first sign[26] (Fig. 32-8). There may be respiratory difficulties and a hoarse cry, due in part to the enlarged tongue; feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking during nursing; an enlarged abdomen; and an umbilical hernia. The manifestations of untreated congenital

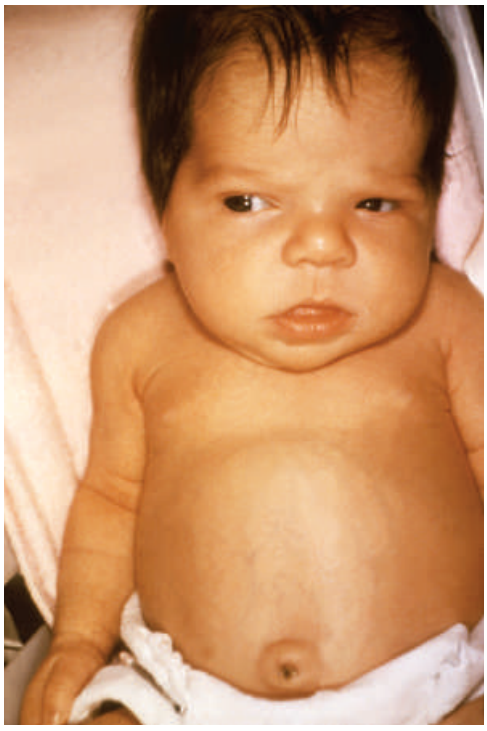

FIGURE 32-8. A 6-week-old female infant who presented with symptoms of jaundice, which was proven to be due to hypothyroidism. She was placed on supplemental thyroid hormonal therapy and appeared to be a normal healthy child at 1 year of age. (From the Centers for Disease Control and Prevention Public Health Images Library. No. 5604.)

hypothyroidism are referred to as *cretinism*. However, the term does not apply to the normally developing infant in whom replacement thyroid hormone therapy was instituted shortly after birth.

Long-term studies have shown that closely monitored T_4 supplementation begun in the first 6 weeks of life results in normal intelligence. Fortunately, developed countries throughout the world now routinely screen newborns for hypothyroidism, providing the means for early diagnosis and treatment. The screening test involves taking a drop of blood from the infant's heel and sending it to a central laboratory, where it is analyzed for T_4 or TSH.[25] Screening is done 24 to 48 hours after birth, usually in the hospital nursery.

Congenital hypothyroidism is treated by hormone replacement. Evidence indicates that it is important to normalize T_4 levels as rapidly as possible because a delay is accompanied by poorer psychomotor and mental development. Dosage levels are adjusted as the child grows.

Transient congenital hypothyroidism has been recognized more frequently since the introduction of neonatal screening. It is characterized by high TSH levels and low or normal thyroid hormone levels. The fetal and infant thyroids are sensitive to iodine excess. Iodine crosses the placenta and mammary glands and is readily absorbed by infant skin.[25] Transient hypothyroidism may be caused by maternal or infant exposure to substances such as povidone-iodine used as a disinfectant (i.e., vaginal douche or skin disinfectant in the nursery). Antithyroid drugs such as propylthiouracil and methimazole can cross the placenta and in large doses will impair fetal thyroid function. Infants with transient hypothyroidism usually can have the replacement therapy withdrawn at 6 to 12 months. When early and adequate treatment regimens are followed, the risk of mental retardation in infants detected by screening programs essentially is nonexistent.

Acquired Hypothyroidism. Hypothyroidism in older children and adults causes a general slowing down of metabolic processes and myxedema.[25] Myxedema implies the presence of a nonpitting mucous type of edema caused by an accumulation of a hydrophilic mucopolysaccharide substance in the connective tissues throughout the body. The hypothyroid state may be mild, with only a few signs and symptoms, or it may progress to a life-threatening condition called *myxedematous coma*. It can result from destruction or dysfunction of the thyroid gland (i.e., primary hypothyroidism), as a secondary disorder caused by impaired pituitary function, or as a tertiary disorder caused by a hypothalamic dysfunction.

Primary hypothyroidism is much more common than secondary (and tertiary) hypothyroidism. It may result from thyroidectomy (i.e., surgical removal) or ablation of the gland with radiation. Certain goitrogenic agents, such as lithium carbonate (used in the treatment of bipolar disorders), and the antithyroid drugs propylthiouracil and methimazole in continuous dosage can block hormone synthesis and produce hypothyroidism with goiter. Large amounts of iodine (i.e., ingestion of kelp tablets or iodide-containing cough syrups, or administration of iodide-containing radiographic contrast media or the cardiac drug amiodarone, which contains 75 mg of iodine per 200-mg tablet) also can block thyroid hormone production and cause goiter, particularly in persons with autoimmune thyroid disease. Iodine deficiency, which can cause goiter and hypothyroidism, is rare in the United States because of the widespread use of iodized salt and other iodide sources.

The most common cause of hypothyroidism is *Hashimoto thyroiditis*, an autoimmune disorder in which the thyroid gland may be totally destroyed by an immunologic process.[28,29] It is the major cause of goiter and hypothyroidism in children and adults. Hashimoto thyroiditis is predominantly a disease of women, with a female-to-male ratio of 5:1. The course of the disease varies. At the onset, only a goiter may be present. In time, hypothyroidism usually becomes evident. Although the disorder usually causes hypothyroidism, a hyperthyroid state may develop midcourse in the disease. The transient hyperthyroid state is caused by leakage of preformed thyroid hormone from damaged cells of the thyroid gland. Subacute thyroiditis, which can occur in up to 10% of pregnancies postpartum (postpartum thyroiditis), also can result in hypothyroidism.

Hypothyroidism may affect almost all body functions (see Table 32-1).[25,29,30] The manifestations of the disorder are related largely to two factors: the hypometabolic state resulting from thyroid hormone deficiency, and myxedematous involvement of body tissues. The hypometabolic state associated with hypothyroidism is characterized by a gradual onset of weakness and fatigue, a tendency to gain weight despite a loss of appetite, and cold intolerance (Fig. 32-9). As the condition progresses, the skin becomes dry and rough and the hair becomes coarse and brittle. Reduced conversion of carotene to vitamin A and increased blood levels of carotene may give the skin a yellowish color. The face becomes puffy with edematous eyelids, and there is thinning of the outer third of the eyebrows. Fluid may collect in almost any serous cavity and in the middle ear, giving rise to conductive deafness. Gastrointestinal motility is decreased, producing constipation, flatulence, and abdominal distention. Delayed relaxation of deep tendon reflexes and bradycardia are sometimes noted. Central nervous system involvement is manifested in mental dullness, lethargy, and impaired memory.

Although the myxedematous fluid is usually most obvious in the face, it can collect in the interstitial spaces of almost any body structure and is responsible for many of the manifestations of the severe hypothyroid state. The tongue is often enlarged, and the voice becomes hoarse and husky. Carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain. Pericardial or pleural effusion may develop. Mucopolysaccharide deposits in the heart cause generalized cardiac dilation, bradycardia, and other signs of altered cardiac function.

Diagnosis of hypothyroidism is based on history, physical examination, and laboratory tests. A low

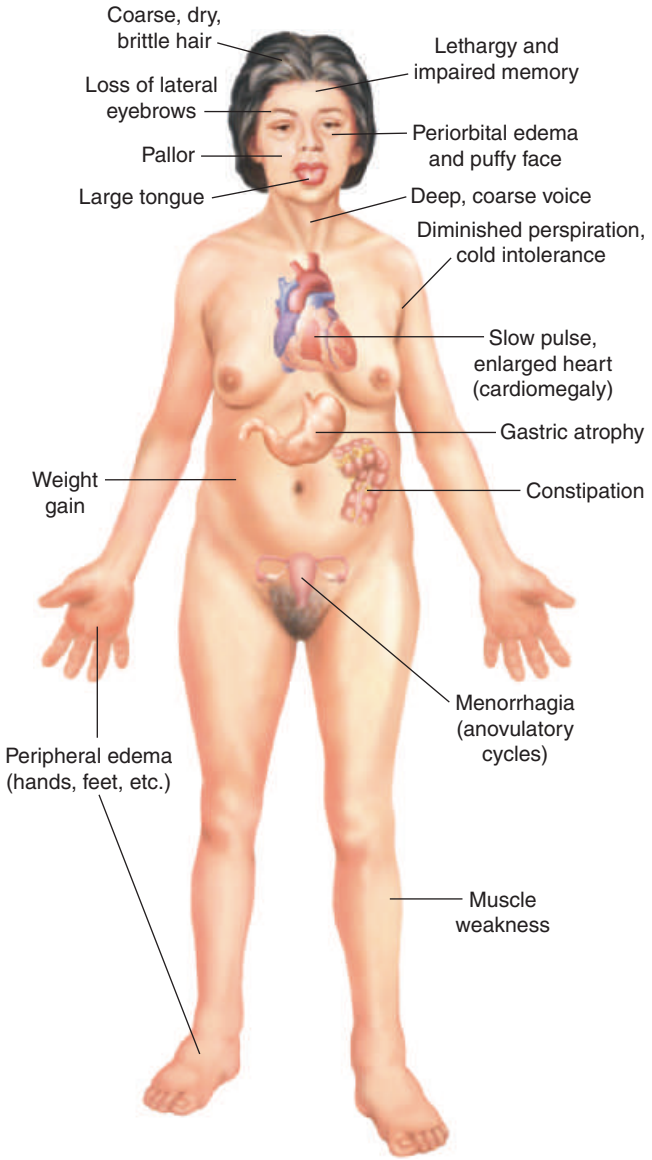

FIGURE 32-9. Clinical manifestations of hypothyroidism.

serum T_4 and elevated TSH levels are characteristic of primary hypothyroidism. The tests for antithyroid antibodies should be done when Hashimoto thyroiditis is suspected (anti-TPO antibody titer is the preferred test).

Hypothyroidism is treated by replacement therapy with synthetic preparations of T_3 or T_4. Most people are treated with T_4. Serum TSH levels are used to estimate the adequacy of T_4 replacement therapy. When the TSH level is normalized, the T_4 dosage is considered satisfactory (for primary hypothyroidism only). A "go low and go slow" approach should be considered in the treatment of elderly persons with hypothyroidism because of the risk of inducing acute coronary syndromes in susceptible individuals.

Myxedematous Coma. Myxedematous coma is a life-threatening, end-stage expression of hypothyroidism.[31] It is characterized by coma, hypothermia, cardiovascular collapse, hypoventilation, and severe metabolic disorders including hyponatremia, hypoglycemia, and lactic acidosis. The pathophysiology of myxedema coma involves three major aspects: (1) carbon dioxide retention and hypoxemia, (2) fluid and electrolyte imbalance, and (3) hypothermia.[31] It occurs most often in elderly women who have chronic hypothyroidism from a spectrum of causes. The fact that it occurs more frequently in winter months suggests that cold exposure may be a precipitating factor. The severely hypothyroid person is unable to metabolize sedatives, analgesics, and anesthetic drugs, and buildup of these agents may precipitate coma.

Treatment includes aggressive management of precipitating factors; supportive therapy such as management of cardiorespiratory status, hyponatremia, and hypoglycemia; and thyroid replacement therapy. If hypothermia is present (a low-reading thermometer should be used), active rewarming of the body is contraindicated because it may induce vasodilation and vascular collapse. Prevention is preferable to treatment and entails special attention to high-risk populations, such as women with a history of Hashimoto thyroiditis. These persons should be informed about the signs and symptoms of severe hypothyroidism and the need for early medical treatment.

Hyperthyroidism

Hyperthyroidism is the clinical syndrome that results when tissues are exposed to high levels of circulating thyroid hormone. In most instances, hyperthyroidism is due to hyperactivity of the thyroid gland.[25,32,33] The most common causes of hyperthyroidism are Graves' disease (to be discussed) and diffuse goiter. Other causes of hyperthyroidism are multinodular goiter, adenoma of the thyroid, and thyroiditis. Iodine-containing agents can induce hyperthyroidism as well as hypothyroidism. Thyroid crisis, or storm, is an acutely exaggerated manifestation of the thyrotoxic state.

Many of the manifestations of hyperthyroidism are related to the increase in oxygen consumption and use of metabolic fuels associated with the hypermetabolic state, as well as to the increase in sympathetic nervous system activity that occurs (see Table 32-1).[25,32,33] The fact that many of the signs and symptoms of hyperthyroidism resemble those of excessive sympathetic nervous system activity suggests that thyroid hormone may heighten the sensitivity of the body to the catecholamines or that it may act as a pseudocatecholamine. With the hypermetabolic state, there are frequent complaints of nervousness, irritability, and fatigability (Fig. 32-10). Weight loss is common despite a large appetite. Other manifestations include tachycardia, palpitations, shortness of breath, excessive sweating, muscle cramps, and heat intolerance. The person appears restless and has a fine muscle tremor. Even in persons without exophthalmos (i.e., bulging of the eyeballs seen in Graves' disease), there is an abnormal retraction of the eyelids and infrequent blinking such that they appear to be staring. The hair and skin usually are thin and have a silky appearance. About 15%

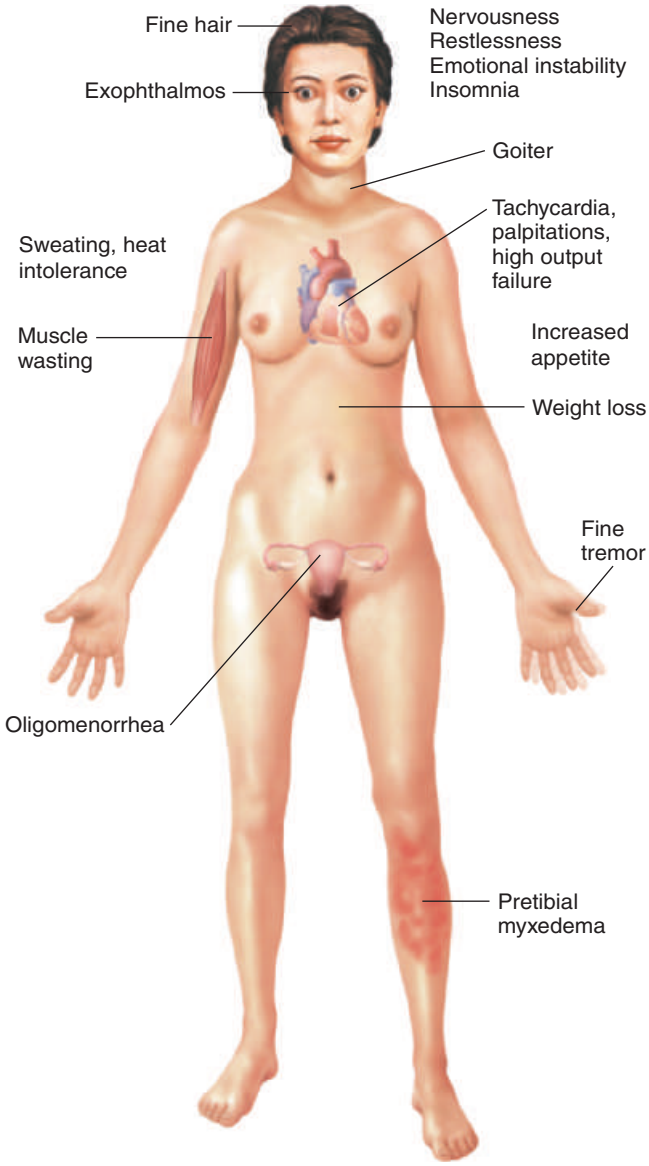

FIGURE 32-10. Clinical manifestations of hyperthyroidism.

of elderly individuals with new-onset atrial fibrillation have thyrotoxicosis.[32]

The treatment of hyperthyroidism is directed toward reducing the level of thyroid hormone. This can be accomplished with eradication of the thyroid gland with radioactive iodine, through surgical removal of part or all of the gland, or with the use of drugs that decrease thyroid function and thereby the effect of thyroid hormone on the peripheral tissues. Eradication of the thyroid with radioactive iodine is used more frequently than surgery. The β-adrenergic blocking drugs (e.g., propranolol, metoprolol, atenolol, nadolol) are administered to block the effects of the hyperthyroid state on sympathetic nervous system function. They are given in conjunction with antithyroid drugs (e.g., propylthiouracil and methimazole) that act by inhibiting the thyroid gland from using iodine in thyroid hormone synthesis and by blocking the conversion of T_4 to T_3 in the tissues (propylthiouracil only).

Graves' Disease. Graves' disease is an autoimmune disorder characterized by abnormal stimulation of the thyroid gland by thyroid-stimulating antibodies (TSH-receptor antibodies) that act through the normal TSH receptors. Identified by Irish surgeon Robert James Graves, it may be associated with other autoimmune disorders such as myasthenia gravis and pernicious anemia. The disease is associated with human leukocyte antigen (HLA)-DR3 and HLA-B8, and a familial tendency is evident. The onset usually is between the ages of 20 and 40 years, and women are five times more likely to develop the disease than men.

Graves' disease is characterized by a triad of hyperthyroidism, goiter, ophthalmopathy (exophthalmos), or less commonly, dermopathy (pretibial edema due to accumulation of fluid and glycosaminoglycans).[25,34–37] The ophthalmopathy, which occurs in up to one third of persons with Graves' disease (Fig. 32-11), is thought to result from a cytokine-mediated activation of fibroblasts in orbital tissue behind the eyeball. Humoral autoimmunity also is important; an ophthalmic immunoglobulin may exacerbate lymphocytic infiltration of the extraocular muscles. The ophthalmopathy of Graves' disease can cause severe eye problems, including abnormal positioning of the extraocular muscles resulting in diplopia; involvement of the optic nerve, with some visual loss; and corneal ulceration because the lids do not close over the protruding eyeball (due to the exophthalmos). The ophthalmopathy usually tends to stabilize after treatment of the hyperthyroidism. Since the ophthalmopathy can worsen acutely

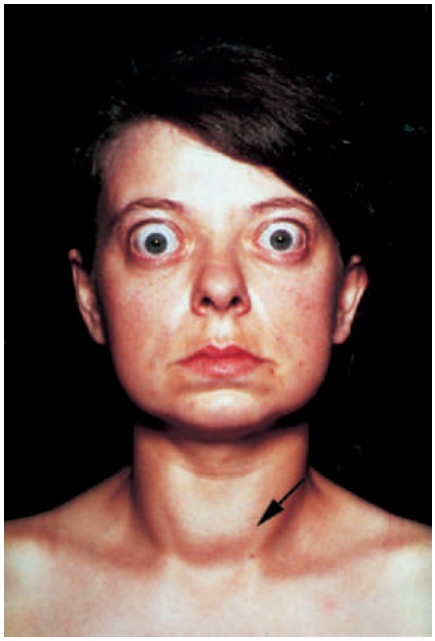

FIGURE 32-11. Graves' disease. A young woman with hyperthyroidism displays a mass in the neck and exophthalmos. (From: Merino MJ, Quezado M. The endocrine system. In: Rubin R, Strayer DS, eds. *Rubin's Pathology: Clinicopathologic Foundations of Medicine,* 6th ed. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2012:1050. Courtesy of Novartis International AG.)

after radioiodine treatment, some physicians prescribe glucocorticoids for several weeks surrounding the radioiodine treatment if the person had signs of ophthalmopathy. Others do not use radioiodine therapy under these circumstances, but prefer antithyroid therapy with drugs (which may decrease the immune activation in the condition). Unfortunately, not all of the ocular changes are reversible with treatment. Ophthalmopathy also can be aggravated by smoking, which should be strongly discouraged.

Thyroid Storm. Thyroid storm, or crisis, is an extreme and life-threatening form of thyrotoxicosis, rarely seen today because of improved diagnosis and treatment methods.[25,38] When it does occur, it is seen most often in undiagnosed cases or in persons with hyperthyroidism who have not been adequately treated. It often is precipitated by stress such as an infection (usually respiratory), diabetic ketoacidosis, physical or emotional trauma, or manipulation of a hyperactive thyroid gland during thyroidectomy. Thyroid storm is manifested by a very high fever, extreme cardiovascular effects (i.e., tachycardia, congestive failure, and angina), and severe CNS effects (i.e., agitation, restlessness, and delirium). The mortality rate is high.

Thyroid storm requires rapid diagnosis and implementation of treatment. Peripheral cooling is initiated with cold packs and a cooling mattress. For cooling to be effective, the shivering response must be prevented. General supportive measures to replace fluids, glucose, and electrolytes are essential during the hypermetabolic state. A β-adrenergic blocking drug, such as propranolol, is used to block the undesirable effects of T_4 on cardiovascular function. Glucocorticoids are used to correct the relative adrenal insufficiency resulting from the stress imposed by the hyperthyroid state and to inhibit the peripheral conversion of T_4 to T_3. Propylthiouracil or methimazole may be given to block thyroid synthesis. Aspirin increases the level of free thyroid hormones by displacing the hormones from their protein carriers and should not be used during thyroid storm.

SUMMARY CONCEPTS

- Thyroid hormones play a major role in the metabolic processes of almost all body cells and are necessary for normal physical and mental growth in infants and young children. Disorders of thyroid function can manifest as a hypothyroid or a hyperthyroid state.
- Hypothyroidism can occur as a congenital or an acquired defect. Congenital hypothyroidism leads to mental retardation and impaired physical growth unless treatment is initiated during the first months of life. When hypothyroidism occurs in older children or adults, it produces a hypometabolic state, an accumulation of a hydrophilic mucopolysaccharide substance (myxedema) in the connective tissues throughout the body, and an elevation in serum cholesterol. There is a gradual onset of weakness, a tendency to gain weight despite a loss of appetite, and cold intolerance. As the condition progresses, the skin becomes dry and rough, the hair becomes brittle, and the face becomes puffy with edematous eyelids.
- Myxedematous coma, which is manifested by coma, hypothermia, severe fluid and electrolyte imbalances, and cardiovascular collapse, is a life-threatening, end-stage expression of hypothyroidism.
- Hyperthyroidism has an effect opposite to that of hypothyroidism. It produces an increase in metabolic rate and oxygen consumption, increased use of metabolic fuels, and increased sympathetic nervous system responsiveness. Manifestations include nervousness, irritability, a fine muscle tremor, weight loss despite an increased appetite, excessive sweating, muscle cramps, and heat intolerance. Graves' disease is characterized by the triad of hyperthyroidism, goiter, and ophthalmopathy (exophthalmos or protruding eyeballs) or dermopathy (pretibial myxedema).
- Thyroid storm or crisis, which is manifested by a very high fever, extreme cardiovascular effects (tachycardia, congestive failure, and angina), and severe central nervous system effects (agitation, restlessness, and delirium), is an extreme and life-threatening form of thyrotoxicosis.

Adrenal Cortical Hormone Disorders

The adrenal glands are small, bilateral structures that weigh approximately 5 g each and lie retroperitoneally at the apex of each kidney (Fig. 32-12A). The medulla or inner portion of the gland (which constitutes approximately 10% of each adrenal) secretes epinephrine and norepinephrine and is part of the sympathetic nervous system. The cortex forms the bulk of the adrenal gland (approximately 90%) and is responsible for secreting three types of hormones: glucocorticoids, mineralocorticoids, and adrenal androgens.[26,39] Because the sympathetic nervous system also secretes the neurotransmitters epinephrine and norepinephrine, adrenal medullary function is not essential for life, but adrenal cortical function is. If untreated, the total loss of adrenal cortical function is fatal in 4 to 14 days.