CHAPTER
31

Alterations in Pituitary, Thyroid, Parathyroid, and Adrenal Function

The endocrine system affects all aspects of body function, including growth and development, energy metabolism, muscle and adipose tissue distribution, sexual development, fluid and electrolyte balance, and inflammation and immune responses. This chapter focuses on disorders of pituitary function, growth and growth hormone levels, thyroid function, and adrenocortical function.

GENERAL ASPECTS OF ALTERED ENDOCRINE FUNCTION

Hypofunction and Hyperfunction

Disturbances of endocrine function usually can be divided into two categories: hypofunction and hyperfunction. Hypofunction of an endocrine gland can occur for a variety of reasons. Congenital defects can result in the absence or impaired development of the gland or the absence of an enzyme needed for hormone synthesis. The gland may be destroyed by a disruption in blood flow, infection, inflammation, autoimmune responses, or neoplastic growth. There may be a decline in function with aging, or the gland may atrophy as the result of drug therapy or for unknown reasons. Some endocrine-deficient states are associated with receptor defects: hormone receptors may be absent, the receptor binding of hormones may be defective, or the cellular response to the hormone may be impaired. It is suspected that in some cases a gland may produce a biologically inactive

hormone or that an active hormone may be destroyed by circulating antibodies before it can exert its action.

Hyperfunction usually is associated with excessive hormone production. This can result from excessive stimulation and hyperplasia of the endocrine gland or from a hormone-producing tumor of the gland. An ectopic tumor can produce hormones; for example, certain bronchogenic tumors produce hormones such as antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH).

Primary, Secondary, and Tertiary Disorders

Endocrine disorders in general can be divided into primary, secondary, and tertiary groups. *Primary defects* in endocrine function originate in the target gland responsible for producing the hormone. In *secondary disorders* of endocrine function, the target gland is essentially normal, but its function is altered by defective levels of stimulating hormones or releasing factors from the pituitary system. For example, adrenalectomy produces a primary deficiency of adrenal corticosteroid hormones. Removal or destruction of the pituitary gland eliminates ACTH stimulation of the adrenal cortex and brings about a secondary deficiency. A *tertiary disorder* results from hypothalamic dysfunction (as may occur with craniopharyngiomas or cerebral irradiation); thus, both the pituitary and target organ are understimulated.

In summary, endocrine disorders are the result of hypofunction or hyperfunction of an endocrine gland. They can occur as a primary defect in hormone production by a target gland or as a secondary or tertiary disorder resulting from a defect in the hypothalamic-pituitary system that controls a target gland's function.

PITUITARY AND GROWTH HORMONE DISORDERS

The anterior lobe of the pituitary gland produces ACTH, thyroid stimulating hormone (TSH), growth hormone (GH), the gonadotrophic hormones (follicle stimulating hormone [FSH] and luteinizing hormone [LH]), and prolactin (see Chapter 30, Fig. 30-4). Four of these, ACTH, TSH, LH, and FSH control the secretion of hormones from other endocrine glands. ACTH controls the release of cortisol from the adrenal gland and TSH the secretion of thyroid hormone from the thyroid gland; LH regulates sex hormones, and FSH regulates fertility.

Hypopituitarism

Hypopituitarism, which is characterized by a decreased secretion of pituitary hormones, is a condition that affects many of the other endocrine systems. Typically, 70% to 90% of the anterior pituitary must be destroyed before hypopituitarism becomes clinically evident.[1] The cause may be congenital or result from a variety of acquired abnormalities (Chart 31-1). The manifestations of hypopituitarism usually occur gradually, but it can present as an acute and life-threatening condition. Patients usually report being chronically unfit, with weakness, fatigue, loss of appetite, impairment of sexual function, and cold intolerance. However, ACTH deficiency (secondary adrenal failure) is the most serious endocrine deficiency, leading to weakness, nausea, anorexia, fever, and postural hypotension. Hypopituitarism is associated with increased morbidity and mortality.

CHART 31-1 Causes of Hypopituitarism

- Tumors and mass lesions—pituitary adenomas, cysts, metastatic cancer, and other lesions
- Pituitary surgery or radiation
- Infiltrative lesions and infections—hemochromatosis, lymphocytic hypophysitis
- Pituitary infarction—infarction of the pituitary gland after substantial blood loss during childbirth (Sheehan's syndrome)
- Pituitary apoplexy—sudden hemorrhage into the pituitary gland
- Genetic diseases—rare congenital defects of one or more pituitary hormones
- Empty sella syndrome—an enlarged sella turcica that is not entirely filled with pituitary tissue
- Hypothalamic disorders—tumors and mass lesions (*e.g.,* craniopharyngiomas and metastatic malignancies), hypothalamic radiation, infiltrative lesions (*e.g.,* sarcoidosis), trauma, infections

Anterior pituitary hormone loss tends to follow a typical sequence, especially with progressive loss of pituitary reserve caused by tumors or previous pituitary radiation therapy (which may take 10 to 20 years to produce hypopituitarism). Usually GH secretion is lost first, then LH and FSH, followed by TSH deficiency. ACTH is usually the last to become deficient.

Treatment of hypopituitarism includes treating any identified underlying cause. Hormone deficiencies are treated with replacement of the target gland hormone. Cortisol replacement is started when ACTH deficiency is present; thyroid replacement when TSH deficiency is detected; and sex hormone replacement when LH and FSH are deficient. GH replacement is being used increasingly to treat GH deficiency.

Growth and Growth Hormone Disorders

Several hormones are essential for normal body growth and maturation, including growth hormone (GH), insulin, thyroid hormone, and androgens. In addition to its actions on carbohydrate and fat metabolism, insulin plays an essential role in growth processes. Children with diabetes, particularly those with poor control, often fail to grow normally even though GH levels are normal. When levels of thyroid hormone are lower than normal, bone growth and epiphyseal closure are delayed. Androgens such as testosterone and dihydrotestosterone exert anabolic growth effects through their actions on protein synthesis. Glucocorticoids at excessive levels inhibit growth, apparently because of their antagonistic effect on GH secretion.

Growth Hormone

Growth hormone, also called *somatotropin*, is a 191–amino-acid polypeptide hormone synthesized and secreted by special cells in the anterior pituitary called *somatotropes*. For many

years, it was thought that GH was produced primarily during periods of growth. However, this has proved to be incorrect because the rate of GH production in adults is almost as great as in children. GH is necessary for growth and contributes to the regulation of metabolic functions (Fig. 31-1).[2,3] All aspects of cartilage growth are stimulated by GH; one of the most striking effects of GH is on linear bone growth, resulting from its action on the epiphyseal growth plates of long bones. The width of bone increases because of enhanced periosteal growth; visceral and endocrine organs, skeletal and cardiac muscle, skin, and connective tissue all undergo increased growth in response to GH. In many instances, the increased growth of visceral and endocrine organs is accompanied by enhanced functional capacity. For example, increased growth of cardiac muscle is accompanied by an increase in cardiac output.

In addition to its effects on growth, GH facilitates the rate of protein synthesis by all of the cells of the body; it enhances fatty acid mobilization and increases the use of fatty acids for fuel; and it maintains or increases blood glucose levels by decreasing the use of glucose for fuel. GH has an initial effect of increasing insulin levels. However, the predominant effect of prolonged GH excess is to increase glucose levels despite an insulin increase. This is because GH induces a resistance to insulin in the peripheral tissues, inhibiting the uptake of glucose by muscle and adipose tissues.

Many of the effects of GH depend on a family of peptides called *insulin-like growth factors* (IGF), also called *somatomedins*, which are produced mainly by the liver. GH cannot directly produce bone growth; instead, it acts indirectly by causing the liver to produce IGF. These peptides act on cartilage and bone to promote their growth. At least four IGFs have been identified; of these, IGF-1 appears to be the more important in terms of growth, and it is the one that usually is measured in laboratory tests. The IGFs have been sequenced and have structures that are similar to that of proinsulin. This undoubtedly explains the insulin-like activity of the IGFs and the weak action of insulin on growth. IGF levels are themselves influenced by a family of at least six binding factors called *IGF-binding proteins* (IGFBPs).

GH is carried unbound in the plasma and has a half-life of approximately 20 to 50 minutes. The secretion of GH is regulated by two hypothalamic hormones: GH-releasing hormone (GHRH), which increases GH release, and somatostatin, which inhibits GH release. A third hormone, the recently identified ghrelin, also may be important. These hypothalamic influences (*i.e.*, GHRH and somatostatin) are tightly regulated by neural, metabolic, and hormonal factors. The secretion of GH fluctuates during a 24-hour period, with peak levels occurring 1 to 4 hours after onset of sleep (*i.e.*, during sleep stages 3 and 4). The nocturnal sleep bursts, which account for 70% of daily GH secretion, are greater in children than in adults.[4]

GH secretion is stimulated by hypoglycemia, fasting, starvation, increased blood levels of amino acids (particularly arginine), and stress conditions such as trauma, excitement, emotional stress, and heavy exercise. GH is inhibited by increased glucose levels, free fatty acid release, cortisol, and obesity. Impairment of secretion, leading to growth retardation, is not uncommon in children with severe emotional deprivation.

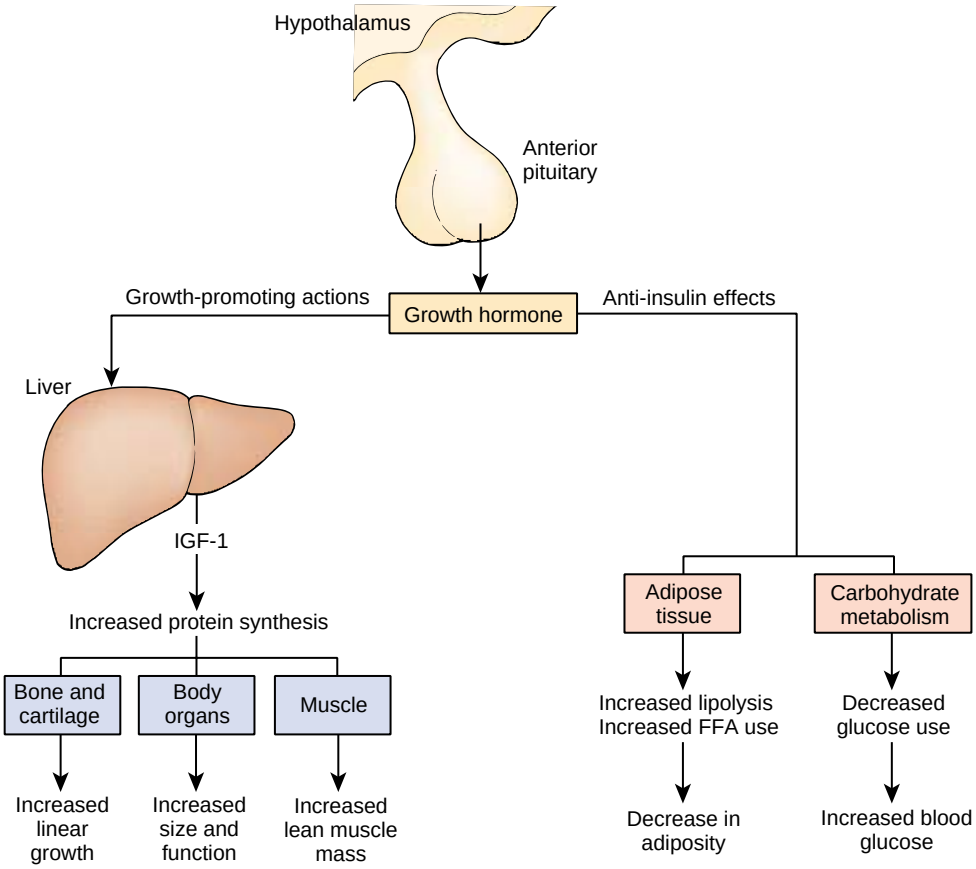


FIGURE 31-1 Growth-promoting and anti-insulin effects of growth hormone. IGF-1, insulin growth factor 1.

KEY CONCEPTS

GROWTH HORMONE

- Growth hormone (GH), which is produced by somatotropes in the anterior pituitary, is necessary for linear bone growth in children. It also stimulates cells to increase in size and divide more rapidly; it enhances amino acid transport across cell membranes and increases protein synthesis; and it increases the rate at which cells use fatty acids and decreases the rate at which they use carbohydrates.
- The effects of GH on cartilage growth require insulin-like growth factors (IGFs), also called *somatomedins*, which are produced mainly by the liver.
- In children, GH deficiency interferes with linear bone growth, resulting in short stature or dwarfism. In a rare condition called *Laron-type dwarfism*, GH levels are normal or elevated, but there is a hereditary defect in IGF production.
- GH excess in children results in increased linear bone growth, or gigantism. In adults, GH excess results in overgrowth of the cartilaginous parts of the skeleton, enlargement of the heart and other organs of the body, and metabolic disturbances resulting in altered fat metabolism and impaired glucose tolerance.

CHART 31-2 Causes of Short Stature

Variants of Normal

Genetic or "familial" short stature
Constitutional short stature

Low Birth Weight (*e.g.*, intrauterine growth retardation)

Endocrine Disorders

Growth hormone (GH) deficiency
  Primary GH deficiency
    Idiopathic GH deficiency
    Pituitary agenesis
  Secondary GH deficiency (panhypopituitarism)
  Biologically inactive GH production
  Deficient IGF-1 production in response to normal or elevated GH (Laron-type dwarfism)
Hypothyroidism
Diabetes mellitus in poor control
Glucocorticoid excess
  Endogenous (Cushing's disease)
  Exogenous (glucocorticoid drug treatment)
Abnormal mineral metabolism (*e.g.*, pseudohypoparathyroidism)

Chronic Illness and Malnutrition

Chronic organic or systemic disease (*e.g.*, asthma, especially when treated with glucocorticoids; heart or renal disease)
Nutritional deprivation
Malabsorption syndrome

Functional Endocrine Disorders (Psychosocial Dwarfism)

Chromosomal Disorders (*e.g.*, Turner's Syndrome)

Skeletal Abnormalities (*e.g..*, achondroplasia)

Short Stature and Growth Hormone Deficiency in Children

Short stature is a condition in which the attained height is well below the fifth percentile or linear growth is below normal for age and gender. Short stature, or growth retardation, has a variety of causes, including chromosomal abnormalities such as Turner's syndrome (see Chapter 4), GH deficiency, hypothyroidism, and panhypopituitarism. Other conditions known to cause short stature include protein-calorie malnutrition, chronic diseases such as renal failure and poorly controlled diabetes mellitus, malabsorption syndromes, and certain therapies such as corticosteroid administration. Emotional disturbances can lead to functional endocrine disorders, causing psychosocial dwarfism. The causes of short stature are summarized in Chart 31-2.

Accurate measurement of height is an extremely important part of the physical examination of children. Completion of the developmental history and growth charts is essential. Growth curves and growth velocity studies also are needed. Diagnosis of short stature is not made on a single measurement but is based on actual height and on velocity of growth and parental height. The diagnostic procedures for short stature include tests to exclude nonendocrine causes. Extensive hormonal testing procedures are initiated in cases where an endocrine cause is suspected. Usually, tests to determine GH and IGF-1 levels are done. Radiologic films are used to assess bone age, which most often is delayed. Lateral skull x-rays may be used to evaluate the size and shape of the sella turcica (*i.e.*, depression in the sphenoid bone that contains the pituitary gland) and determine if a pituitary tumor exists. Magnetic resonance imaging (MRI) or computed axial tomography (CT) scans of the hypothalamic-pituitary area may be done if a pituitary lesion is suspected. After the cause of short stature has been determined, treatment can be initiated.

Genetic and Constitutional Short Stature. Two forms of short stature, genetic short stature and constitutional short stature, are not disease states but variations from population norms.[5] Genetically short children tend to be well proportioned and to have a height close to the midparental height of their parents. The midparental height for boys can be calculated by adding 13 cm (5 inches) to the height of the mother, adding the father's height, and dividing the total by two. For girls, 13 cm (5 inches) is subtracted from the father's height, the result is added to the mother's height, and the total is divided by two. Ninety-five percent of normal children are within 8.5 cm of the midparental height.

Constitutional short stature is a term used to describe children (particularly boys) who have moderately short stature, thin

build, delayed skeletal and sexual maturation, and absence of other causes of decreased growth. *Catch-up growth* is a term used to describe an abnormally high growth rate that occurs as a child approaches normal height for age. It occurs after the initiation of therapy for GH deficiency and hypothyroidism and the correction of chronic diseases.

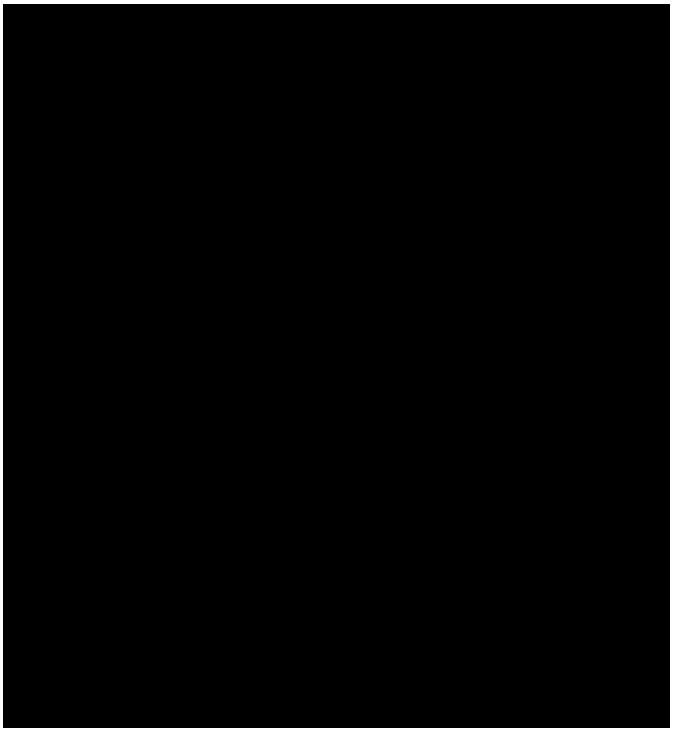
Psychosocial Dwarfism. Psychosocial dwarfism involves a functional hypopituitarism and is seen in some emotionally deprived children. These children usually present with poor growth, potbelly, and poor eating and drinking habits.[5,6] Typically, there is a history of disturbed family relationships in which the child has been severely neglected or disciplined. Often, the neglect is confined to one child in the family. GH function usually returns to normal after the child is removed from the constraining environment. The prognosis depends on improvement in behavior and catch-up growth. Family therapy usually is indicated, and foster care may be necessary.

Growth Hormone Deficiency in Children. There are several forms of GH deficiency that present in childhood. Children with idiopathic GH deficiency lack the hypothalamic GHRH but have adequate somatotropes, whereas children with pituitary tumors or agenesis of the pituitary lack somatotropes. The term *panhypopituitarism* refers to conditions that cause a deficiency of all of the anterior pituitary hormones. In a rare condition called *Laron-type dwarfism*, GH levels are normal or elevated, but there is a hereditary defect in IGF production that can be treated directly with IGF-1 replacement.[7]

Congenital GH deficiency is associated with normal birth length, followed by a decrease in growth rate that can be identified by careful measurement during the first year and that becomes obvious by 1 to 2 years of age. Persons with classic GH deficiency have normal intelligence, short stature, obesity with immature facial features, and some delay in skeletal maturation (Fig. 31-2). Puberty often is delayed, and males with the disorder have microphallus (abnormally small penis), especially if the condition is accompanied by gonadotropin-releasing hormone (GnRH) deficiency. In the neonate, GH deficiency can lead to hypoglycemia and seizures; if adrenocorticotropic hormone (ACTH) deficiency also is present, the hypoglycemia often is more severe. Acquired GH deficiency develops in later childhood; it may be caused by a hypothalamic-pituitary tumor, particularly if it is accompanied by other pituitary hormone deficiencies.

When short stature is due to a GH deficiency, GH replacement therapy is the treatment of choice. GH is species specific, and only human GH (hGH) is effective in humans. Human GH, which is synthesized by recombinant DNA techniques, is now available in adequate supply. It is administered subcutaneously in multiple weekly doses during the period of active growth, and its use can be continued into adulthood.

Children with short stature due to Turner's syndrome and chronic renal insufficiency also are treated with hGH.[8] hGH therapy may be considered for children with short stature but without GH deficiency. Several studies suggest that short-term treatment with GH increases the rate of growth in these children. Although the effect of GH on adult height is not great, it can result in improved psychological well-being. There are concerns about misuse of the drug to produce additional growth in children with normal GH function who are of near-



normal height. Guidelines for use of the hormone continue to be established.

Growth Hormone Deficiency in Adults

There are two categories of GH deficiency in adults: (1) GH deficiency that was present in childhood, and (2) GH deficiency that developed during adulthood, mainly as the result of hypopituitarism resulting from a pituitary tumor or its treatment. GH levels also can decline with aging, and there has been interest in the effects of declining GH levels in the elderly (described as the *somatopause*).

Several studies have shown that cardiovascular mortality is increased in GH-deficient adults.[9] Increased arterial intima-media thickness and a higher prevalence of atherosclerotic plaques and endothelial dysfunction have been reported in both childhood and adult GH deficiency. The GH deficiency syndrome is associated with a cluster of cardiovascular risk factors, including central adiposity (increased waist-hip ratio), increased visceral fat, insulin resistance, and dyslipidemia. These features also are associated with the *metabolic syndrome* (syndrome X; see Chapter 32). In addition to these so-called traditional cardiovascular risk factors, nontraditional cardiovascular risk factors (*e.g.*, C-reactive protein and interleukin-6, which are markers of the inflammatory pathway) also are elevated.

The diagnosis of GH deficiency in adults is made by finding subnormal serum GH responses to two stimulation tests that measure GH reserve. Measurements of the serum IGF-1 or basal GH do not distinguish reliably between normal and subnormal GH secretion in adults. Insulin-induced hypoglycemia is the gold standard test for GH reserve. The L-dopa test probably is the next best test. Other stimulation tests involve the use of arginine or arginine plus GHRH, clonidine (an α-adrenergic agonist), glucagon, or GHRH.

GH replacement obviously is important in the growing child; however, the role in adults (especially for the somato-

pause) is being assessed. Adults with documented GH deficiency may be treated with hGH. In the United States, persons with GH deficiency acquired as an adult must meet at least two criteria for therapy: a poor GH response to at least two standard stimuli, and hypopituitarism caused by pituitary or hypothalamic damage.[8]

Tall Stature and Growth Hormone Excess in Children

Tall Stature. Just as there are children who are short for their age and sex, there also are children who are tall for their age and sex. Normal variants of tall stature include genetic tall stature and constitutional tall stature. Children with exceptionally tall parents tend to be taller than children with shorter parents. The term *constitutional tall stature* is used to describe a child who is taller than his or her peers and is growing at a velocity that is within the normal range for bone age.[5,10] Other causes of tall stature are genetic or chromosomal disorders, such as Marfan's syndrome or XYY syndrome (see Chapter 4). Endocrine causes of tall stature include sexual precocity because of early onset of estrogen and androgen secretion and excessive GH.

Exceptionally tall children (*i.e.*, genetic tall stature and constitutional tall stature) can be treated with sex hormones—estrogens in girls and testosterone in boys—to effect early epiphyseal closure. Such treatment is undertaken only after full consideration of the risks involved. To be effective, such treatment must be instituted 3 to 4 years before expected epiphyseal fusion.

Gigantism. Growth hormone excess occurring before puberty and the fusion of the epiphyses of the long bones results in gigantism (Fig. 31-3). Excessive secretion of GH by somatotrope adenomas causes gigantism in the prepubertal child. It occurs when the epiphyses are not fused and high levels of IGF stimulate excessive skeletal growth. Fortunately, the condition is rare because of early recognition and treatment of the adenoma.

Growth Hormone Excess in Adults

When GH excess occurs in adulthood or after the epiphyses of the long bones have fused, the condition is referred to as *acromegaly*.[11] Acromegaly results from excess levels of GH that stimulate the hepatic secretion of IGF-1, which causes most of the clinical manifestations of acromegaly. The annual incidence of acromegaly is 3 to 4 cases per 1 million people, with a mean age at the time of diagnosis of 40 to 45 years.

The most common cause of acromegaly is a somatotrope adenoma. Approximately 75% of persons with acromegaly have large expansive tumors that erode the sella turcica and impinge on adjacent cranial structures, and most of the remainder have small tumors contained within the pituitary gland. Other causes of acromegaly (<5%) are excess secretion of GHRH by hypothalamic tumors, ectopic GHRH secretion by nonendocrine tumors such as carcinoid tumors or small cell lung cancers, and ectopic secretion of GH by nonendocrine tumors.

The disorder usually has an insidious onset, and symptoms often are present for a considerable period before a diagnosis is made. When the production of excessive GH occurs after the epiphyses of the long bones have closed, as in the adult, the person cannot grow taller, but the soft tissues continue to grow. Enlargement of the small bones of the hands and feet and of the membranous bones of the face and skull results in a pronounced enlargement of the hands and feet, a broad and bulbous nose, a protruding lower jaw, and a slanting forehead. The teeth become splayed, causing a disturbed bite and difficulty in chewing. The cartilaginous structures in the larynx and respiratory tract also become enlarged, resulting in a deepening of the voice and tendency to develop bronchitis. Vertebral changes often lead to kyphosis, or hunchback. Bone overgrowth often leads to arthralgias and degenerative arthritis of the spine, hips, and knees. Virtually every organ of the body is increased in size. Enlargement of the heart and accelerated atherosclerosis may lead to an early death.

The metabolic effects of excess levels of GH include alterations in fat and carbohydrate metabolism. GH causes increased release of free fatty acids from adipose tissue, leading to increased concentration of free fatty acids in body fluids. In addition, GH enhances the formation of ketones and the utilization of free fatty acids for energy in preference to use of carbohydrates and proteins. GH exerts multiple effects on carbohydrate metabolism, including decreased glucose uptake by tissues such as skeletal muscle and adipose tissue, increased glucose production by the liver, and increased insulin secretion. Each of these changes results in GH-induced insulin resistance (see Chapter 32). This leads to glucose intolerance, which stimulates the beta cells of the pancreas to produce additional insulin. Long-term elevation of GH results in

overstimulation of the beta cells, causing them literally to "burn out." Impaired glucose tolerance occurs in as many as 50% to 70% of persons with acromegaly; overt diabetes mellitus subsequently can result.

The pituitary gland is located in the pituitary fossa of the sphenoid bone (*i.e.*, sella turcica), which lies directly below the optic nerve. Enlargement of the pituitary gland eventually causes erosion of the surrounding bone, and because of its location, this can lead to headaches, visual field defects resulting from compression of the optic nerve, and palsies of cranial nerves III, IV, and VI. Compression of other pituitary structures can cause secondary hypothyroidism, hypogonadism, and adrenal insufficiency. Other manifestations include excessive sweating with an unpleasant odor, oily skin, heat intolerance, moderate weight gain, muscle weakness and fatigue, menstrual irregularities, and decreased libido. Hypertension is relatively common. Paresthesias may develop because of nerve entrapment and compression caused by excess soft tissue and accumulation of subcutaneous fluid (especially carpal tunnel syndrome). Acromegaly also is associated with an increased risk of colonic polyps and colorectal cancer. The mortality rate of patients with acromegaly is two to three times the expected rate, mostly from cardiovascular diseases and cancer. The cardiovascular disease results from the combination of cardiomyopathy, hypertension, insulin resistance and hyperinsulinemia, and hyperlipidemia.

Acromegaly often develops insidiously, and only a small number of persons seek medical care because of changes in appearance. The diagnosis of acromegaly is facilitated by the typical features of the disorder—enlargement of the hands and feet and coarsening of facial features. Laboratory tests to detect elevated levels of GH not suppressed by a glucose load are used to confirm the diagnosis. CT and MRI scans can detect and localize the pituitary lesions. Because most of the effects of GH are mediated by IGF-1, IGF-1 levels may provide information about disease activity.

The treatment goals for acromegaly focus on the correction of metabolic abnormalities and include normalization of the GH response to an oral glucose load; normalization of IGF-1 levels to age- and gender-matched control levels; removal or reduction of the tumor mass; relieving the central pressure effects; improvement of adverse clinical features; and normalization of the mortality rate.[12] Pituitary tumors can be removed surgically using the transsphenoidal approach or, if that is not possible, a transfrontal craniotomy. Radiation therapy may be used, but remission (reduction in GH levels) may not occur for several years after therapy. Radiation therapy also significantly increases the risk of hypopituitarism, hypothyroidism, hypoadrenalism, and hypogonadism.[5]

Medications used for the treatment of acromegaly include the somatostatin analogs, which produce feedback inhibition of GH. Sustained-release preparations, which effectively inhibit GH secretion for 30 days after a single intramuscular injection, are now available.[4]

Isosexual Precocious Puberty

Sexual development is considered precocious and warrants investigation when it occurs before 8 years of age for girls and before 9 years of age for boys. Precocious sexual development may be idiopathic or may be caused by gonadal, adrenal, or hypothalamic tumors. True isosexual precocious puberty is caused by early activation of the hypothalamic-pituitary-gonadal axis. The gonadotropin-mediated increase in size and activity of the gonads leads to increasing sex hormone production with early development of sexual characteristics and fertility.[13,14] 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. Gonadotropin-independent causes of precocious puberty include functioning ovarian tumors and feminizing adrenal tumors in girls and congenital adrenal hyperplasia and Leydig cell tumors in boys.[13]

Diagnosis of precocious puberty 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. CT or MRI should be used to exclude intracranial lesions.

Depending on the cause of precocious puberty, the treatment may involve surgery, medication, or no treatment. The treatment of choice for gonadotropin-dependent precocious puberty is administration of a long-acting GnRH agonist. Constant levels of the hormone cause a decrease in pituitary responsiveness to GnRH, leading to decreased secretion of gonadotropic hormones and sex steroids. 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.

In summary, hypopituitarism, which is characterized by a decreased secretion of pituitary hormones, is a condition that affects many of the other endocrine systems. Depending on the extent of the disorder, it can result in decreased levels of GH, thyroid hormones, adrenal corticosteroid hormones, and testosterone in the male and of estrogens and progesterone in the female.

A number of hormones are essential for normal body growth and maturation, including GH, insulin, thyroid hormone, and androgens. GH exerts its growth effects through a group of IGFs. GH also exerts an effect on metabolism and is produced in the adult and in the child. Its metabolic effects include a decrease in peripheral use of carbohydrates and an increased mobilization and use of fatty acids.

In children, alterations in growth include short stature, tall stature, and isosexual precocious puberty. Short stature is a condition in which the attained height is well below the fifth percentile or the linear growth velocity is below normal for a child's age or gender. Short stature can occur as a variant of normal growth (*i.e.*, genetic short stature or constitutional short stature) or as the result of endocrine disorders, chronic illness, malnutrition, emotional disturbances, or chromosomal disorders. Short stature resulting from GH deficiency can be treated with human GH preparations. 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. GH levels also can decline with aging,

and there has been interest in the effects of declining GH levels in the elderly (described as the *somatopause*).

Tall stature refers to the condition in which children are tall for their age and gender. It 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. GH excess in adults results in acromegaly, which involves proliferation of bone, cartilage, and soft tissue along with the metabolic effects of excessive hormone levels.

Isosexual precocious puberty defines a condition of early activation of the hypothalamic-pituitary-gonadal axis (*i.e.*, before 8 years of age in girls and 9 years of age in boys), resulting in the development of appropriate 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 DISORDERS

Control of Thyroid Function

The thyroid gland is a shield-shaped structure located immediately below the larynx in the anterior middle portion of the neck. It is composed of a large number of tiny, saclike structures called *follicles* (Fig. 31-4). 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-iodine complex called *thyroglobulin*.

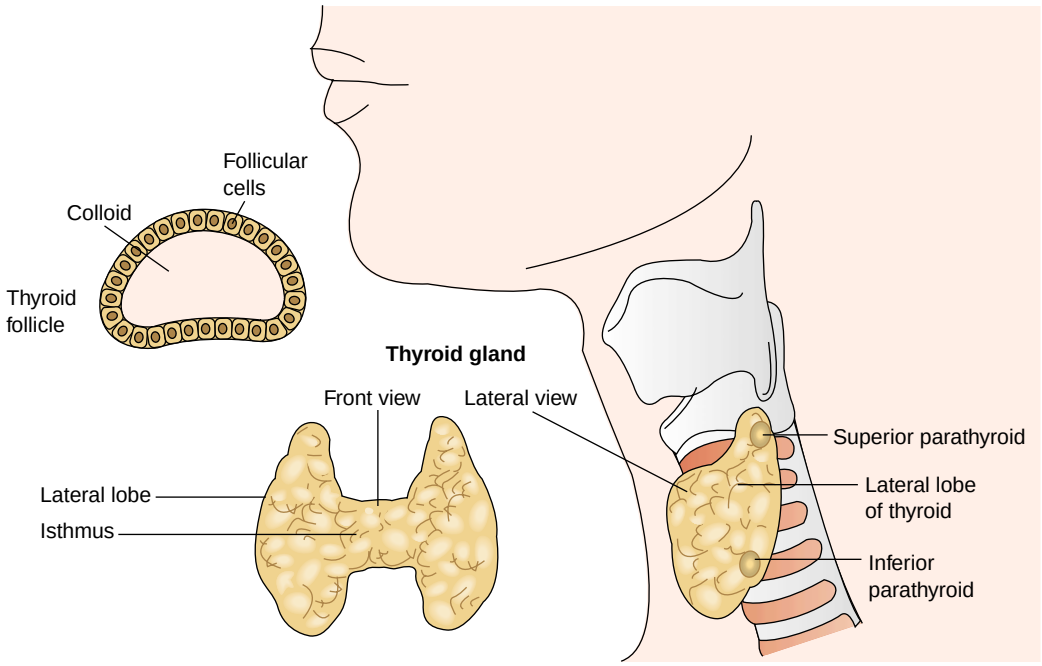
The thyroglobulin that fills the thyroid follicles is a large glycoprotein molecule that contains 140 tyrosine amino acids. In the process of thyroid synthesis, iodine is attached to these tyrosines. Both thyroglobulin and iodide are secreted into the colloid of the follicle by the follicular cells.

The thyroid is remarkably efficient in its use of iodide. A daily absorption of 100 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 is pumped into the follicular cells against a concentration gradient. As a result, the concentration of iodide in the normal thyroid gland is approximately 30 times that in the blood.[2]

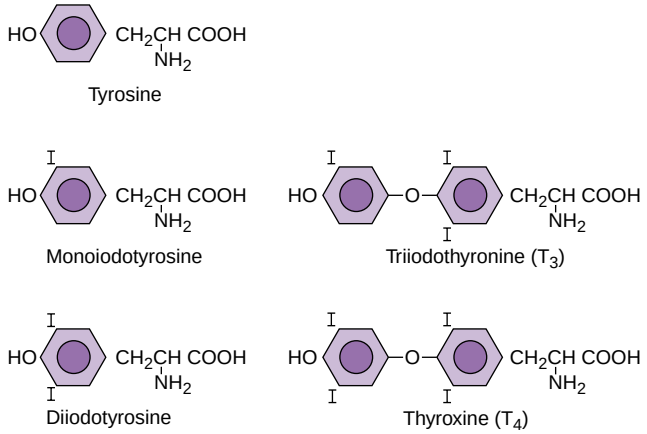
Once inside the follicle, most of the iodide is oxidized by the enzyme peroxidase in a reaction that facilitates combination with a tyrosine molecule to form monoiodotyrosine and then diiodotyrosine (Fig. 31-5). Two diiodotyrosine residues are coupled to form thyroxine (T_4), or a monoiodotyrosine and a diiodotyrosine are coupled to form triiodothyronine (T_3). Only T_4 (93%) and T_3 (7%) are released into the circulation.[2] 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 thyroid-binding globulin and other plasma proteins 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. There are three major thyroid-binding proteins: thyroid hormone-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin. More than 99% of T_4 and T_3 is carried in the bound form. TBG carries approximately 70% of T_4 and T_3; TBPA 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 disease conditions and pharmacologic agents can decrease the amount of binding protein in the plasma or influence the binding of hormone. Congenital TBG deficiency



■ **FIGURE 31-4** ■ The thyroid gland and the follicular structure.

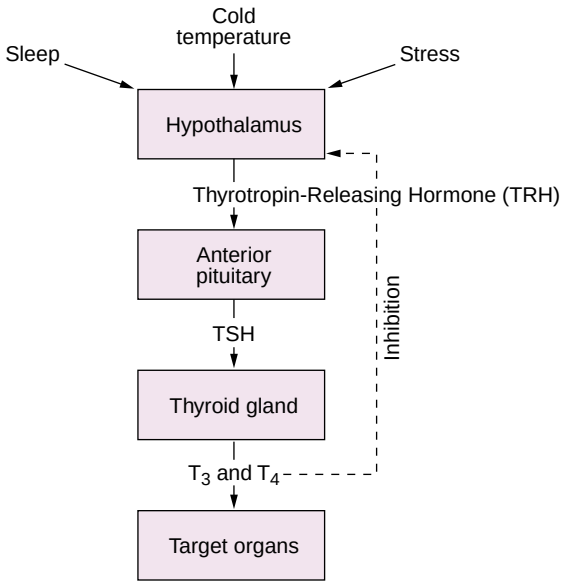


■ **FIGURE 31-5** ■ Chemistry of thyroid hormone production.

is an X-linked trait that occurs in 1 of every 2500 live births. Corticosteroid medications and systemic disease conditions such as protein malnutrition, nephrotic syndrome, and cirrhosis decrease TBG concentrations. Medications such as phenytoin, salicylates, and diazepam may bind to TBG, displacing T_4 and T_3, effectively producing a low TBG state.

The secretion of thyroid hormone is regulated by the hypothalamic-pituitary-thyroid feedback system (Fig. 31-6). In this system, thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus, controls the release of thyroid-stimulating hormone (TSH) from the anterior pituitary gland. TSH, in turn, increases the overall activity of the thyroid gland by promoting the release of thyroid hormone into the bloodstream and increasing T_4 and T_3 synthesis. The effect of TSH on the release of thyroid hormones occurs within approximately 30 minutes, but the other effects require days or weeks.

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.



■ **FIGURE 31-6** ■ The hypothalamic-pituitary-thyroid feedback system, which regulates the body levels of thyroid hormone.

Actions of Thyroid Hormone

All the major organs in the body are affected by altered levels of thyroid hormone. Thyroid hormone has two major functions: it increases metabolism and protein synthesis, and it is necessary for growth and development in children, including mental development and attainment of sexual maturity.

Metabolic Rate. Thyroid hormone increases the metabolism of all body tissues except the retina, spleen, testes, and lungs. The basal metabolic rate can increase by 60% to 100% above normal when large amounts of T_4 are present.[2] 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 the metabolic rate "speeds up" the use of vitamins and tends to cause vitamin deficiency.

Cardiovascular Function. Cardiovascular and respiratory functions are strongly affected by thyroid function. With an increase in metabolism, there is an increase in oxygen consumption and production of metabolic end-products, with an accompanying increase in vasodilatation. Blood flow to the skin, in particular, is augmented as a means of dissipating the body heat that results from the higher metabolism. Blood volume, cardiac output, and ventilation all are increased as a means of maintain-

KEY CONCEPTS

THYROID HORMONE

- Thyroid hormone increases the metabolism and protein synthesis in nearly all of the tissues of the body.
- Hypothyroidism produces a decrease in metabolic rate, an accumulation of a hydrophilic mucopolysaccharide substance (myxedema) in the connective tissues throughout the body, and an elevation in serum cholesterol.
- Hyperthyroidism has an effect opposite that of hypothyroidism. It produces an increase in metabolic rate and oxygen consumption, increased use of metabolic fuels, and increased sympathetic nervous ystem responsiveness.

ing blood flow and oxygen delivery to body tissues. Heart rate and cardiac contractility are enhanced as a means of maintaining the needed cardiac output. However, blood pressure is likely to change little because the increase in vasodilatation 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

The diagnosis of thyroid disorders is based on tests of T_3, T_4, and TSH levels, radioiodine uptake studies, thyroid scans, ultrasound, and CT or MRI scans.[15] 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. Ultrasensitive TSH measurements are used to diagnose hyperthyroidism and hypothyroidism, as well 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 (via negative feedback) is elevated.

The radioiodine (^{123}I) uptake test measures the ability of the thyroid gland to remove and concentrate iodine from the blood. Thyroid scans (*i.e.*, ^{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.

Alterations in Thyroid Function

An alteration in thyroid function can represent a hypofunctional or a hyperfunctional state. The manifestations of these two altered states are summarized in Table 31-1. Disorders of the thyroid may be caused by a congenital defect in thyroid development, or they may develop later in life, with a gradual or sudden onset.

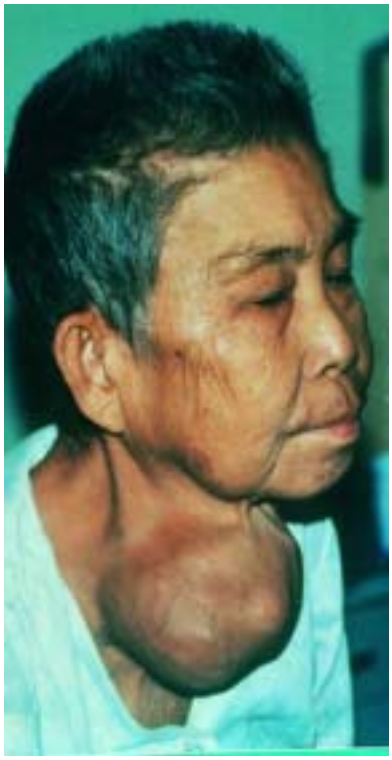
Goiter is an increase in the size of the thyroid gland. It can occur in hypothyroid, euthyroid, and hyperthyroid states.

TABLE 31-1 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 Deep voice Impaired growth (child)	Exophthalmos Lid lag Decreased blinking
Blood cholesterol levels	Increased	Decreased
General behavior	Mental retardation (infant) Mental and physical sluggishness Somnolence	Restlessness, irritability, anxiety Hyperkinesis Wakefulness
Cardiovascular function	Decreased cardiac output Bradycardia	Increased cardiac output Tachycardia and palpitations
Gastrointestinal function	Constipation Decreased appetite	Diarrhea Increased appetite
Respiratory function	Hypoventilation	Dyspnea
Muscle tone and reflexes	Decreased	Increased, with tremor and fibrillatory twitching
Temperature tolerance	Cold intolerance	Heat intolerance
Skin and hair	Decreased sweating Coarse and dry skin and hair	Increased sweating Thin and silky skin and hair
Weight	Gain	Loss

Goiters may be diffuse, involving the entire gland without evidence of nodularity, or they may contain nodules. Diffuse goiters usually become nodular. Goiters may be toxic, producing signs of extreme hyperthyroidism, or thyrotoxicosis, or they may be nontoxic. Diffuse nontoxic and multinodular goiters are the result of compensatory hypertrophy and hyperplasia of follicular epithelium from some derangement that impairs thyroid hormone output (Fig. 31-7).

The degree of thyroid enlargement usually is proportional to the extent and duration of thyroid deficiency. Multinodular goiters produce the largest thyroid enlargements and often are associated with thyrotoxicosis. 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.



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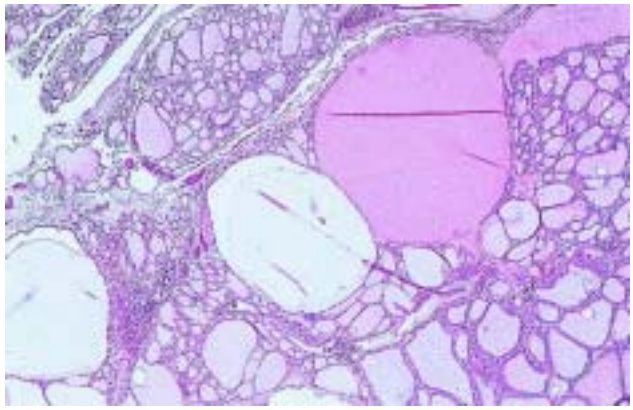


B

■ **FIGURE 31-7** ■ (**A**) Middle-aged woman with a nontoxic (nodular) goiter that has enlarged to produce a conspicuous neck mass. (**B**) Microscopic view of one of the macroscopic nodules shows marked variation in size of the follicles. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1164]. Philadelphia: Lippincott Williams & Wilkins)

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

Congenital hypothyroidism is a common cause of preventable mental retardation. It affects approximately 1 of 4000 infants.[16] Hypothyroidism in the infant may result from a congenital lack of the thyroid gland, abnormal biosynthesis of thyroid hormone, or deficient TSH secretion. With congenital lack of the thyroid gland, the infant usually appears normal and functions normally at birth because of the transplacental passage of moderate amounts of maternal T_4. The manifestations of untreated congenital 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.

Thyroid hormone is essential for normal brain development and growth, almost half of which occurs during the first 6 months of life. If untreated, congenital hypothyroidism causes mental retardation and impairs growth. Fortunately, neonatal screening tests have been instituted to detect congenital hypothyroidism during early infancy. Screening usually is done in the hospital nursery. In this test, a drop of blood is taken from the infant's heel and analyzed for T_4 and TSH.

Transient congenital hypothyroidism has been recognized more frequently since the introduction of neonatal screening. It is characterized by high TSH levels and low 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. Transient hypothyroidism may be caused by maternal or infant exposure to substances such as topical iodine-containing disinfectants (*e.g.*, iodine-containing douches or nursery disinfectants). Antithyroid drugs such as propylthiouracil, methimazole, and carbimazole also cross the placenta and block fetal thyroid function.

Congenital hypothyroidism is treated by hormone replacement. Evidence indicates that it is important to normalize T_4 levels as rapidly as possible (in the first 6 weeks of life) because a delay is accompanied by poorer psychomotor and mental development. Dosage levels are adjusted as the child grows. 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 and Myxedema

Acquired hypothyroidism in older children and adults represents a decrease in thyroid function resulting from destruction or dysfunction of the thyroid gland (*i.e.*, primary hypothyroidism)

or impaired hypothalamic or pituitary function (*i.e.*, secondary hypothyroidism).

Primary hypothyroidism is much more common than secondary hypothyroidism. It may result from thyroidectomy (*i.e.*, surgical removal) or ablation of the gland with radiation. Certain goitrogenic agents, such as lithium carbonate (*i.e.*, used in the treatment of manic-depressive states) and the antithyroid drugs propylthiouracil and methimazole in continuous dosage can block hormone synthesis and produce hypothyroidism with goiter. Iodine-containing drugs (*e.g.*, kelp tablets, iodide-containing cough syrups, radiographic contrast media) also can block thyroid hormone production, particularly in persons with autoimmune thyroid disease. Amiodarone (an antiarrhythmic drug), which contains 75 mg of iodine per 200-mg tablet, is being increasingly implicated in causing thyroid problems. 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.

Hashimoto's thyroiditis is an autoimmune disorder in which the thyroid gland may be totally destroyed by an immunologic process.[1] It is the major cause of goiter and hypothyroidism in children and adolescents.[16] Hashimoto's thyroiditis is predominantly a disease of women, with a female-to-male ratio of 10:1 to 20:1.[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 gland.

Clinical Manifestations. The clinical manifestations of hypothyroidism can range from mild nonspecific complaints associated with subclinical hypothyroidism to those associated with overt hypothyroidism.[17] The manifestations of the overt hypothyroidism are related largely to two factors: the hypometabolic state resulting from thyroid hormone deficiency, and myxedematous involvement of body tissues.

The hypometabolic state is characterized by a gradual onset of weakness and fatigue, a tendency to gain weight despite a loss of appetite, and cold intolerance. As the condition progresses, the skin becomes dry and rough and acquires a pale yellowish cast, which primarily results from carotene deposition, and the hair becomes coarse and brittle. There can be loss of the lateral one third of the eyebrows. Gastrointestinal motility is decreased, producing constipation, flatulence, and abdominal distention. Nervous system involvement is manifested in mental dullness, lethargy, and impaired memory.

Myxedema represents 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. As a result of myxedematous fluid accumulation, the face takes on a characteristic puffy look, especially around the eyes, the tongue becomes enlarged, and the voice hoarse and husky (Fig. 31-8). Mucopolysaccharide deposits in the heart can cause generalized cardiac dilatation, bradycardia, and other signs of altered cardiac function. The signs and symptoms of hypothyroidism are summarized in Table 31-1.

Diagnosis and Treatment. Diagnosis of hypothyroidism is based on history and physical examination and laboratory measurement of TSH and free T_4 levels. The condition is treated with replacement therapy using 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.

Myxedematous Coma. Myxedematous coma is a life-threatening, end-stage expression of hypothyroidism. It is characterized by coma, hypothermia, cardiovascular collapse, hypoventilation, and severe metabolic disorders that include hyponatremia, hypoglycemia, and lactic acidosis.[18] It occurs most often in elderly women who have chronic hypothyroidism from a spectrum of causes. It occurs more frequently in the winter months, which 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. Prevention is preferable to treatment and entails special attention to high-risk populations, such as women with a history of Hashimoto's thyroiditis. These persons should be informed about the signs and symptoms of severe hypothyroidism and the need for early medical treatment.

Hyperthyroidism

Hyperthyroidism, or thyrotoxicosis, results from excessive delivery of thyroid hormone to the peripheral tissues. The most common cause of hyperthyroidism is Graves' disease, which is accompanied by ophthalmopathy (exophthalmos, *i.e.*, bulging of the eyeballs) and goiter. Other causes of hyperthyroidism

are multinodular goiter, adenoma of the thyroid, and occasionally, ingestion of excessive thyroid hormone. Thyroid crisis, or storm, is an acutely exaggerated manifestation of the hyperthyroid state.

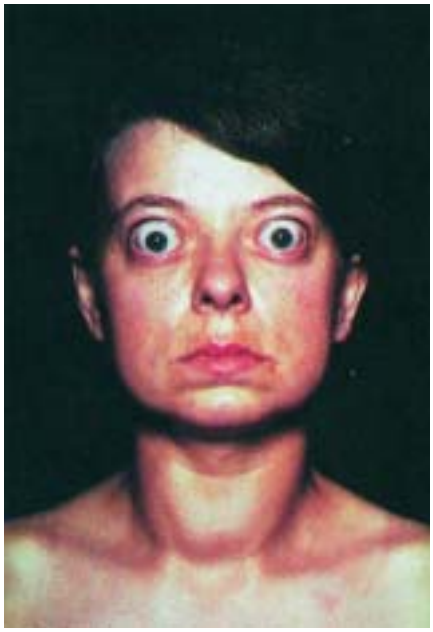
Many of the manifestations of hyperthyroidism are related to the increase in oxygen consumption and use of metabolic fuels associated with the hypermetabolic state, as well as to the increase in sympathetic nervous system activity. With the hypermetabolic state, there are frequent complaints of nervousness, irritability, and fatigability. 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, 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. The signs and symptoms of hyperthyroidism are summarized in Table 31-1.

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 the use of drugs that decrease thyroid function and thereby the effect of thyroid hormone on the peripheral tissues. Destruction of thyroid tissue with radioactive iodine is used more frequently than surgery. The β-adrenergic–blocking drug propranolol may be used to block the effects of the hyperthyroid state on sympathetic nervous system function. It is given in conjunction with other antithyroid drugs such as propylthiouracil and methimazole. These drugs prevent the thyroid gland from converting iodine to its organic (hormonal) form and block the conversion of T_4 to T_3 in the tissues.

Graves' Disease

Graves' disease is a state of hyperthyroidism, goiter, and ophthalmopathy (or, less commonly, dermopathy).[19,20] The onset usually is between the ages of 20 and 40 years, and women are five times more likely to experience the disease than men. Graves' disease is an autoimmune disorder characterized by abnormal stimulation of the thyroid gland by thyroid-stimulating antibodies (thyroid-stimulating immunoglobulins [TSI]) that act through the normal TSH receptors. 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 exophthalmos, which occurs in as many as one third of persons with Graves' disease, is thought to result from thyroid-stimulating antibodies sensitized to interact with antigens found in fibroblasts in orbital tissue behind the eyeball and in the extraocular muscles that move the eyeball.[21,22] The ophthalmopathy of Graves' disease can cause severe eye problems, including paralysis of the extraocular muscles; involvement of the optic nerve, with some visual loss; and corneal ulceration because the lids do not close over the protruding eyeball. The exophthalmos usually tends to stabilize after treatment of the hyperthyroidism. Unfortunately, not all of the ocular changes are reversible with treatment. Smoking tends to aggravate the condition. Figure 31-9 depicts a woman with Graves' disease.



■ **FIGURE 31-9** ■ Graves' disease. A young woman with hyperthyroidism presented with a mass in the neck and exophthalmos. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1167]. Philadelphia: Lippincott Williams & Wilkins)

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. 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). Thyroid storm requires rapid diagnosis and implementation of treatment.

In summary, thyroid hormones play a role in the metabolic process of almost all body cells and are necessary for normal physical and mental growth in the infant and young child. Alterations in 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. Acquired hypothyroidism leads to a decrease in metabolic rate and an accumulation of a mucopolysaccharide substance in the intercellular spaces; this substance attracts water and causes a mucous type of edema called *myxedema*. Hyperthyroidism causes an increase in metabolic rate and alterations in body function similar to those produced by enhanced sympathetic nervous system activity. Graves' disease, which is caused by thyroid-stimulating antibodies, is characterized by hyperthyroidism, goiter, and ophthalmopathy.

PARATHYROID HORMONE DISORDERS

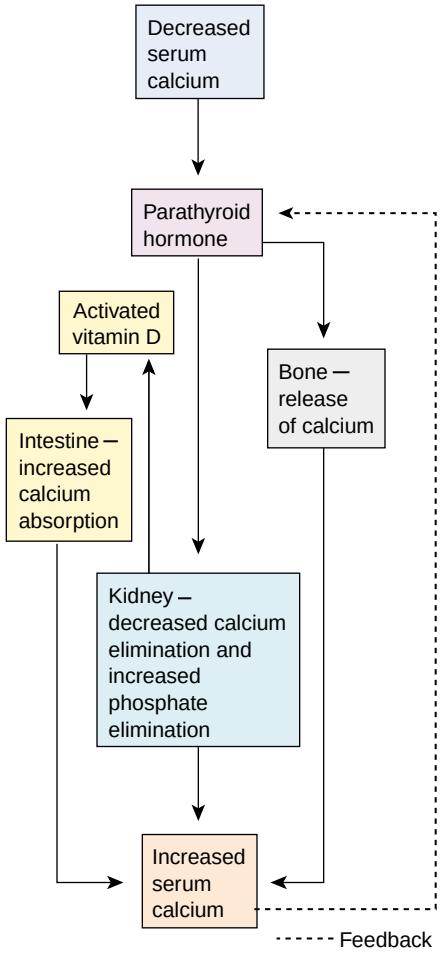
Parathyroid hormone (PTH), a major regulator of serum calcium and phosphate, is secreted by the parathyroid glands. There are four parathyroid glands located on the dorsal surface of the thyroid gland.[1] The dominant regulator of PTH is a decrease in serum calcium concentration. A unique calcium receptor within the parathyroid cell membrane responds rapidly to changes in serum calcium levels. The response to a decrease in serum calcium is prompt, occurring within seconds. Phosphate does not exert a direct effect on PTH secretion. Instead, it acts indirectly by complexing with calcium and decreasing serum calcium concentration.

The secretion, synthesis, and action of PTH are also influenced by magnesium. Magnesium serves as a cofactor in the generation of cellular energy and is important in the function of second messenger systems. Magnesium's effects on the synthesis and release of PTH are thought to be mediated through these mechanisms.[23] Because of its function in regulating PTH release, severe and prolonged hypomagnesemia can markedly inhibit PTH levels.

The main function of PTH is to maintain the calcium concentration of the extracellular fluids. It performs this function by promoting the release of calcium from bone, increasing the activation of vitamin D as a means of enhancing intestinal absorption of calcium, and stimulating calcium conservation by the kidney while increasing phosphate excretion (Fig. 31-10).

Parathyroid hormone acts on bone to accelerate the mobilization and transfer of calcium to the extracellular fluid. The skeletal response to PTH is a two-step process. There is an immediate response in which calcium that is present in bone fluid is released into the extracellular fluid and a second more slowly developing response in which completely mineralized bone is resorbed resulting in the release of both calcium and phosphate The actions of PTH in terms of bone resorption require normal levels of both vitamin D and magnesium.

The activation of vitamin D by the kidney is enhanced by the presence of PTH; it is through the activation of vitamin D that PTH increases intestinal absorption of calcium and phosphate. PTH acts directly on the kidney to increase tubular reabsorption of calcium and magnesium while increasing phosphate elimination. The accompanying increase in phosphate elimination ensures that calcium released from bone does not produce hyperphosphatemia and increase the risk of soft tissue deposition of calcium/phosphate crystals.



■ **FIGURE 31-10** ■ Regulation of serum calcium concentration by parathyroid hormone.

Hypoparathyroidism

Hypoparathyroidism reflects deficient PTH secretion resulting in hypocalcemia. PTH deficiency may be caused by a congenital absence of all of the parathyroid glands, such as occurs in DiGeorge syndrome.[24] An acquired deficiency of PTH may occur after neck surgery, particularly if the surgery involves removal of a parathyroid adenoma, thyroidectomy, or bilateral neck resection for cancer. Hypoparathyroidism may also have an autoimmune origin. Antiparathyroid antibodies have been detected in some persons with hypoparathyroidism, particularly those with multiple endocrine disorders. Other causes of hypoparathyroidism include heavy metal damage, such as occurs with Wilson's disease, metastatic tumors, and infection. Functional impairment of parathyroid function occurs with magnesium deficiency. Correction of the hypomagnesemia results in rapid disappearance of the condition.

Manifestations of acute hypoparathyroidism that result from a decrease in serum calcium include tetany with muscle cramps, carpopedal spasm, and convulsions (see discussion of hypocalcemia in Chapter 6). Paresthesias, such as tingling of the circumoral area and in the hands and feet, are almost always present. There may be prolongation of the QT interval caused by low calcium levels, resistance to digitalis, hypotension, and refractory heart failure. Symptoms of chronic deficiency include lethargy, anxiety state, and personality changes. There may be blurring of vision caused by cataracts, which develop during an extended period of time. Extrapyramidal signs, such as those seen with Parkinson's disease, may occur because of calcification of the basal ganglia. Successful treatment of the hypocalcemia may improve the disorder and is sometimes associated with decreases in basal ganglia calcification on x-ray. Teeth may be defective if the disorder occurs during childhood.

Diagnosis of hypoparathyroidism is based on low serum calcium levels, high serum phosphate levels, and low serum PTH levels. Serum magnesium levels are usually measured to exclude hypomagnesemia as a cause of the disorder.

Acute hypoparathyroid tetany is treated with intravenous calcium gluconate followed by oral administration of calcium salts and vitamin D. Magnesium supplementation is used when the disorder is caused by magnesium deficiency. Persons with chronic hypoparathyroidism are treated with oral calcium and vitamin D. Serum calcium levels are monitored at regular intervals (at least every 3 months) as a means of maintaining serum calcium within a slightly low but asymptomatic range. Maintaining serum calcium within this range helps to prevent hypercalciuria and kidney damage.

Pseudohypoparathyroidism is a rare familial disorder characterized by target tissue resistance to PTH. It is characterized by hypocalcemia, increased parathyroid function, and a variety of congenital defects in the growth and development of the skeleton, including short stature and short metacarpal and metatarsal bones. There are variants in the disorders, with some persons having the pseudohypoparathyroidism with the congenital defects and others having the congenital defects with normal calcium and phosphate levels. The manifestations of the disorder are primarily attributable to hypocalcemia. Treatment is similar to that for hypoparathyroidism.

Hyperparathyroidism

Hyperparathyroidism is caused by hypersecretion of parathyroid hormone. Hyperparathyroidism can manifest as a primary disorder caused by hyperplasia, an adenoma, or carcinoma of the parathyroid glands or as a secondary disorder seen in persons with renal failure.[25]

Primary hyperparathyroidism is seen more commonly after age 50 years and is more common in women than men. Primary hyperparathyroidism causes hypercalcemia and an increase in calcium in the urine filtrate, resulting in hypercalcuria and the potential for development of kidney stones. Chronic bone resorption may produce diffuse demineralization, pathologic fractures, and cystic bone lesions. Signs and symptoms of the disorder are related to skeletal abnormalities, exposure of the kidney to high calcium levels, and elevated serum calcium levels (see hypercalcemia). Diagnostic procedures include serum calcium and parathyroid hormone levels. Imaging studies of the parathyroid area may be used to identify a parathyroid adenoma.

Secondary hyperparathyroidism involves hyperplasia of the parathyroid glands and occurs primarily in persons with renal failure (see Chapter 24).[25] In early renal failure, an increase in PTH results from decreased serum calcium and activated vitamin D levels. As the disease progresses, there is a decrease in vitamin D and calcium receptors, making the parathyroid glands more resistant to vitamin D and calcium. At this point, elevated phosphate levels induce hyperplasia of the parathyroid glands independent of calcium and activated vitamin D.

The bone disease seen in persons with secondary hyperparathyroidism caused by renal failure is known as renal osteodystrophy. Treatment includes resolving the hypercalcemia with large fluid intake. Persons with mild disease are advised to keep active and drink adequate fluids. They also are advised to avoid calcium-containing antacids, vitamin D, and thiazide diuretics, which increase reabsorption of calcium by the kidney. Bisphosphonates (*e.g.*, pamidronate and alendronate), which are potent inhibitors of bone resorption, may be used temporarily to treat the hypercalcemia of hyperparathyroidism. Parathyroidectomy may be indicated in persons with symptomatic hyperthyroidism, kidney stones, or bone disease.

DISORDERS OF ADRENAL CORTICAL FUNCTION

Control of Adrenal Cortical Function

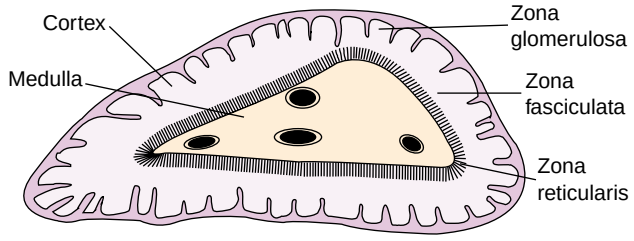
The adrenal glands are small, bilateral structures that weigh approximately 5 g each and lie retroperitoneally at the apex of each kidney (Fig. 31-11). The medulla or inner portion of the gland secretes epinephrine and norepinephrine and is part of the sympathetic nervous system. The cortex forms the bulk of the adrenal gland and is responsible for secreting three types of hormones: the glucocorticoids, the mineralocorticoids, and the adrenal sex hormones. Because the sympathetic nervous system also secretes epinephrine and norepinephrine, adrenal medullary function is not essential for life, but adrenal cortical function is.

Biosynthesis, Transport, and Metabolism

More than 30 hormones are produced by the adrenal cortex. Of these hormones, aldosterone is the principal mineralocorticoid, cortisol (hydrocortisone) is the major glucocorticoid, and androgens are the chief sex hormones.[1] All of the adrenal cortical hormones have a similar structure in that all are steroids and are synthesized from acetate and cholesterol. Each of the steps involved in the synthesis of the various hormones requires a specific enzyme (Fig. 40-11). The secretion of the glucocorticoids and the adrenal androgens is controlled by the ACTH secreted by the anterior pituitary gland.

Cortisol and the adrenal androgens are secreted in an unbound state and bind to plasma proteins for transport in the circulatory system. Cortisol binds largely to corticosteroid-binding globulin and to a lesser extent to albumin. Aldosterone circulates mostly bound to albumin. It has been suggested that the pool of protein-bound hormones may extend the duration of their action by delaying metabolic clearance.

The main site for metabolism of the adrenal cortical hormones is the liver, where they undergo a number of metabolic conversions before being conjugated and made water soluble. They are then eliminated in either urine or bile.



■ **FIGURE 31-11** ■ The adrenal gland, showing the medulla and the three layers of the cortex. The zona glomerulosa is the outer layer of the cortex and is primarily responsible for mineralocorticoid production. The middle layer, the zona fasciculata, and the inner layer, the zona reticularis, produce the glucocorticoids and the adrenal sex hormones.

KEY CONCEPTS

ADRENAL CORTICAL HORMONES

- The adrenal cortex produces three types of steroid hormones: the mineralocorticoids (principally aldosterone), which function in sodium, potassium, and water balance; the glucocorticoids (principally cortisol), which aid in regulating the metabolic functions of the body and in controlling the inflammatory response, and are essential for survival in stress situations; and the adrenal sex hormones (principally androgens), which serve mainly as a source of androgens for women.
- The manifestations of adrenal cortical insufficiency are related mainly to mineralocorticoid deficiency and glucocorticoid deficiency.
- The manifestations of adrenal cortical excess are related to mineralocorticoid excess, glucocorticoid excess with derangements in glucose metabolism and impaired ability to respond to stress because of inhibition of inflammatory and immune responses, and signs of increased androgen levels, such as hirsutism in women.

Adrenal Sex Hormones

The adrenal sex hormones are synthesized primarily by the zona reticularis and the zona fasciculata of the cortex (see Fig. 31-12). These sex hormones probably exert little effect on normal sexual function. However, there is evidence that the adrenal sex hormones (the most important of which is dehydroepiandrosterone) contribute to the pubertal growth of body hair, particularly pubic and axillary hair in women. They also may play a role in the steroid hormone economy of the pregnant woman and the fetal-placental unit.

Mineralocorticoids

The mineralocorticoids play an essential role in regulating potassium and sodium levels and water balance. They are produced in the zona glomerulosa, the outer layer of cells of the adrenal cortex. Aldosterone secretion is regulated by the renin-angiotensin mechanism and by blood levels of potassium. Increased levels of aldosterone promote sodium retention by the distal tubules of the kidney while increasing urinary losses of potassium. The influence of aldosterone on fluid and electrolyte balance is discussed in Chapter 6, and its effect on blood pressure is discussed in Chapter 16.

Glucocorticoids

The glucocorticoid hormones, mainly cortisol, are synthesized in the zona fasciculata and the zona reticularis of the adrenal gland. The blood levels of these hormones are regulated by negative feedback mechanisms of the hypothalamic-pituitary-adrenal (HPA) system (Fig. 31-13). The hypothalamus releases corticotropin-releasing hormone, which is important in controlling the release of ACTH from the pituitary.[1] Cortisol levels increase as ACTH levels rise and decrease as ACTH levels fall. There is considerable diurnal variation in ACTH levels, which reach their peak in the early morning (around 6 to 8 AM) and decline as the day progresses (Fig. 31-14). This appears to be attributable to rhythmic activity in the CNS, which causes bursts of corticotropin-releasing hormone (CRH) secretion and, in turn, ACTH secretion. This diurnal pattern is reversed in people who work during the night and sleep during the day. The rhythm also may be changed by physical and psychological stresses, endogenous depression, manic-depressive psychosis, and liver disease or other conditions that affect cortisol metabolism. One of the earliest signs of Cushing's syndrome, a disorder of cortisol excess, is the loss of diurnal variation in CRH and ACTH secretion.

The glucocorticoids perform a necessary function in response to stress and are essential for survival. When produced as part of the stress response, these hormones aid in regulating the metabolic functions of the body and in controlling the inflammatory response. The actions of cortisol are summarized in Table 31-2.

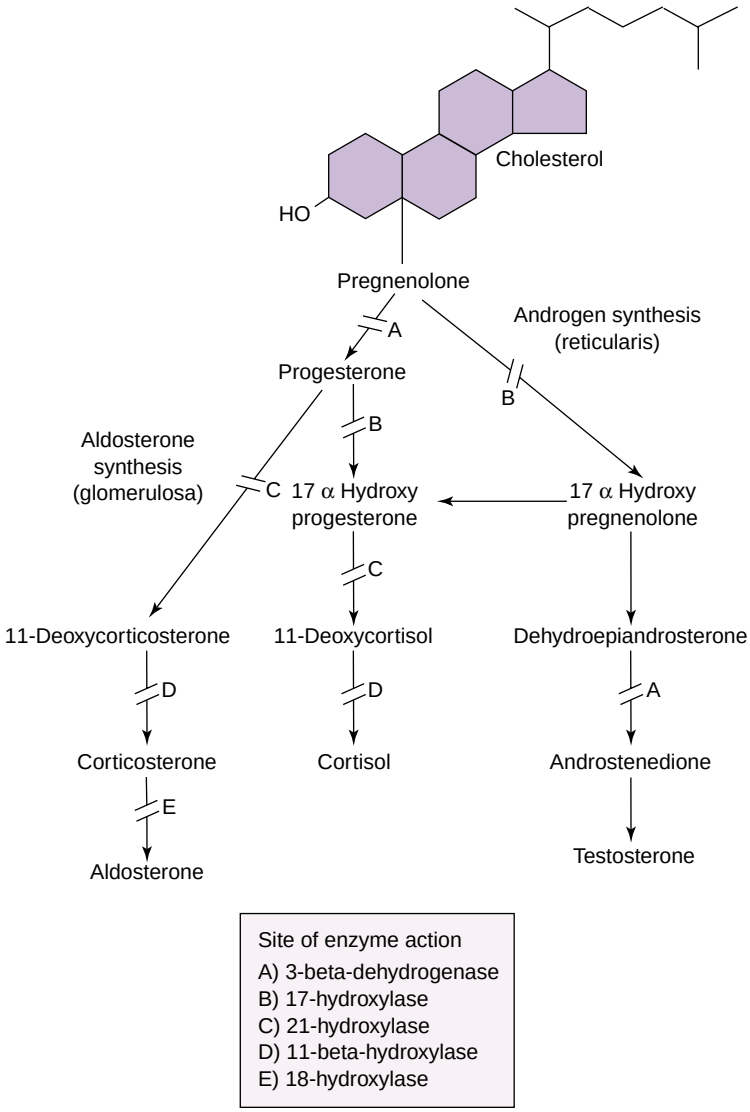
Metabolic Effects. Cortisol stimulates glucose production by the liver, promotes protein breakdown, and causes mobilization of fatty acids. As body proteins are broken down, amino acids are mobilized and transported to the liver, where they are used in the production of glucose (*i.e.*, gluconeogenesis). Mobilization of fatty acids converts cell metabolism from the use of glucose for energy to the use of fatty acids. As glucose production by the liver increases and peripheral glucose use decreases, a moderate resistance to insulin develops. In persons with diabetes and those who are diabetes prone, this has the effect of raising the blood glucose level.

Psychological Effects. The glucocorticoid hormones appear to be involved directly or indirectly in emotional behavior. Receptors for these hormones have been identified in brain tissue, which suggests that they play a role in the regulation of behavior. Persons treated with adrenal cortical hormones have been known to display behavior ranging from mildly aberrant to psychotic.

Immunologic and Inflammatory Effects. Cortisol influences multiple aspects of immunologic function and inflammatory responsiveness. It blocks inflammation at an early stage by decreasing capillary permeability and stabilizing the lysosomal membranes so that inflammatory mediators are not released. Cortisol suppresses the immune response by reducing humoral and cell-mediated immunity. With this lessened inflammatory response comes a reduction in fever. During the healing phase, cortisol suppresses fibroblast activity and thereby lessens scar formation. Cortisol also inhibits prostaglandin synthesis, which may account in large part for its anti-inflammatory actions. Large quantities of cortisol are required for an effective anti-inflammatory action. This is achieved by the administration of pharmacologic, rather than physiologic, doses of synthetic cortisol.

Suppression of Adrenal Function

A highly significant aspect of long-term therapy with pharmacologic preparations of the adrenal cortical hormones is adrenal insufficiency on withdrawal of the drugs. The deficiency



■ **FIGURE 31-12** ■ Predominant biosynthetic pathways of the adrenal cortex. Critical enzymes in the biosynthetic process include 11-beta-hydroxylase and 21-hydroxylase. A deficiency in one of these enzymes blocks the synthesis of hormones dependent on that enzyme and routes the precursors into alternative pathways.

results from suppression of the HPA system. Chronic suppression causes atrophy of the adrenal gland, and the abrupt withdrawal of drugs can cause acute adrenal insufficiency. Recovery to a state of normal adrenal function may be prolonged, requiring 12 months or more.

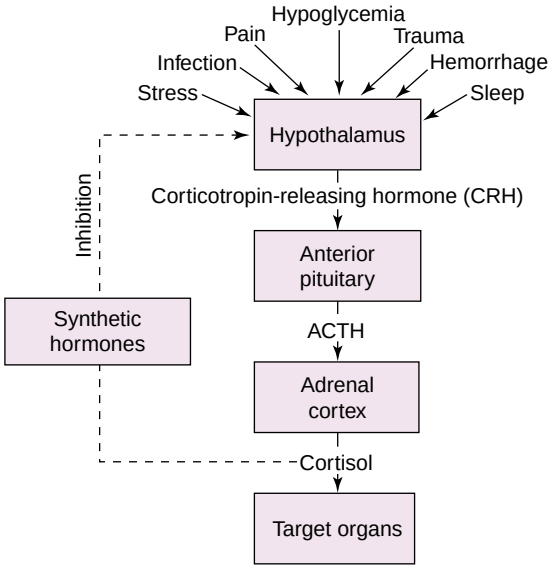
Tests of Adrenal Function

Several diagnostic tests can be used to evaluate adrenal cortical function and the HPA system. Blood levels of cortisol, aldosterone, and ACTH can be measured using immunoassay methods. A 24-hour urine specimen measures the excretion of 17-ketosteroids, 17-ketogenic steroids, and 17-hydroxycorticosteroids. These metabolic end-products of the adrenal hormones and the male androgens provide information about alterations in the biosynthesis of the adrenal cortical hormones. The 24-hour urinary free cortisol is an excellent screening test for Cushing's syndrome.

Suppression and stimulation tests afford a means of assessing the state of the HPA feedback system. For example, a test dose of ACTH can be given to assess the response of the adrenal cortex to stimulation. Similarly, administration of dexamethasone, a synthetic glucocorticoid drug, provides a means of measuring negative feedback suppression of ACTH. Adrenal tumors and ectopic ACTH-producing tumors usually are unresponsive to ACTH suppression by dexamethasone. CRH tests can be used to diagnose a pituitary ACTH-secreting tumor (*i.e.*, Cushing's disease), especially when combined with inferior petrosal venous sampling (this allows the blood drainage of the pituitary to be sampled directly). Metyrapone (Metopirone) blocks the final step in cortisol synthesis, resulting in the production of 11-dehydroxycortisol, which does not inhibit ACTH. This test measures the ability of the pituitary to release ACTH. The gold standard test for assessing the HPA axis is the insulin hypoglycemic stress test.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), or the adrenogenital syndrome, describes a congenital disorder caused by an autosomal recessive trait in which a deficiency exists in any of the



■ **FIGURE 31-13** ■ The hypothalamic-pituitary-adrenal (HPA) feedback system that regulates glucocorticoid (cortisol) levels. Cortisol release is regulated by ACTH. Stress exerts its effects on cortisol release through the HPA system and the corticotropin-releasing hormone (CRH), which controls the release of ACTH from the anterior pituitary gland. Increased cortisol levels incite a negative feedback inhibition of ACTH release. Pharmacologic doses of synthetic steroids inhibit ACTH release by way of the hypothalamic CRH.

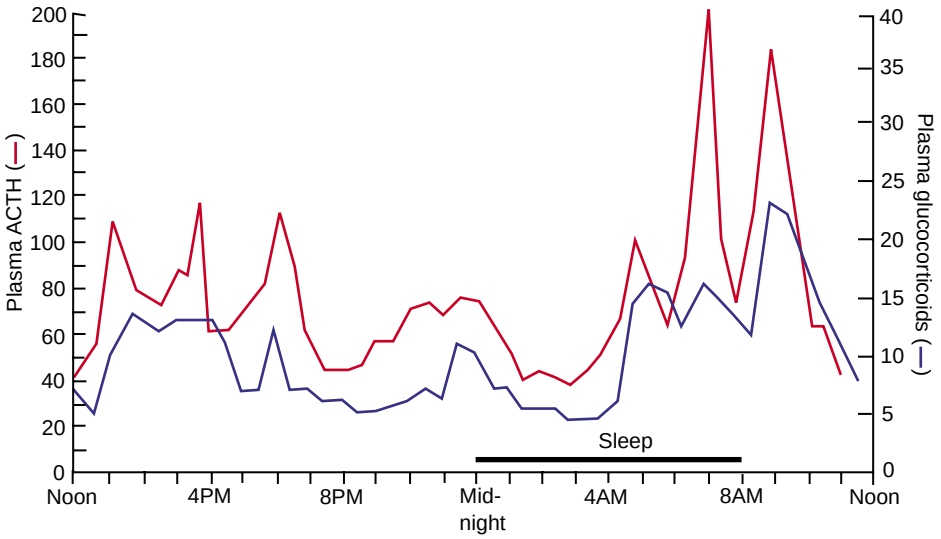
enzymes necessary for the synthesis of cortisol.[26,27] A common characteristic of all types of CAH is a defect in the synthesis of cortisol that results in increased levels of ACTH and adrenal hyperplasia. The increased levels of ACTH overstimulate the pathways for production of adrenal androgens. Mineralocorticoids may be produced in excessive or insufficient amounts, depending on the precise enzyme deficiency. Infants of both genders are affected. The condition is seldom diagnosed in males at birth unless they have enlarged genitalia or lose salt and manifest adrenal crisis. In female infants, an increase in androgens is responsible for creating the virilization syndrome of ambiguous genitalia, with an enlarged clitoris, fused labia, and urogenital sinus (Fig. 31-15). In male and female children, other secondary sex characteristics are normal, and fertility is unaffected if appropriate therapy is instituted.

The two most common enzyme deficiencies are 21-hydroxylase (accounting for >90% of cases) and 11-β-hydroxylase deficiency. The clinical manifestations of both deficiencies are largely determined by the functional properties of the steroid intermediates and the completeness of the block in the cortisol pathway.

A spectrum of 21-hydroxylase deficiency states exists, ranging from simple virilizing CAH to a complete salt-losing enzyme deficiency. Simple virilizing CAH impairs the synthesis of cortisol, and steroid synthesis is shunted to androgen production. Persons with these deficiencies usually produce sufficient aldosterone or aldosterone intermediates to prevent signs and symptoms of mineralocorticoid deficiency. The salt-losing form is accompanied by deficient production of aldosterone and its intermediates. This results in fluid and electrolyte disorders after the fifth day of life, including hyponatremia, hyperkalemia, vomiting, dehydration, and shock.

The 11-β-hydroxylase deficiency is rare and manifests a spectrum of severity. Affected persons have excessive androgen production and impaired conversion of 11-deoxycorticosterone to corticosterone. The overproduction of 11-deoxycorticosterone, which has mineralocorticoid activity, is responsible for the hypertension that accompanies this deficiency. Diagnosis of adrenogenital syndrome depends on the precise biochemical evaluation of metabolites in the cortisol pathway and on clinical signs and symptoms.

Medical treatment of adrenogenital syndrome includes oral or parenteral cortisol replacement. Fludrocortisone acetate, a mineralocorticoid, also may be given to children who are salt losers. Depending on the degree of virilization, reconstructive surgery during the first 2 years of life is indicated to reduce the size of the clitoris, separate the labia, and exteriorize the vagina. Surgery has provided excellent results and does not impair sexual function.



■ **FIGURE 31-14** ■ Pulsatile changes in the concentration of adrenocorticotropic hormone (ACTH) and glucocorticoids over a 24-hour period. The amplitude of the pulses of ACTH and glucocorticoids is lower in the evening hours and then increases greatly during the early morning hours. This is due to the diurnal oscillation of the hypothalamic-pituitary axis. (Modified from Krieger D.T. [1979]. Rhythms of CRF, ACTH and corticosteroids. In Krieger D.T. [Ed.], *Endocrine rhythms* [pp. 123–142]. New York: Raven)

TABLE 31-2 Actions of Cortisol

Major Influence	Effect on Body
Glucose metabolism	Stimulates gluconeogenesis Decreases glucose use by the tissues
Protein metabolism	Increases breakdown of proteins Increases plasma protein levels
Fat metabolism	Increases mobilization of fatty acids Increases use of fatty acids
Anti-inflammatory action (pharmacologic levels)	Stabilizes lysosomal membranes of the inflammatory cells, preventing the release of inflammatory mediators Decreases capillary permeability to prevent inflammatory edema Depresses phagocytosis by white blood cells to reduce the release of inflammatory mediators Suppresses the immune response Causes atrophy of lymphoid tissue Decreases eosinophils Decreases antibody formation Decreases the development of cell-mediated immunity Reduces fever Inhibits fibroblast activity
Psychic effect	May contribute to emotional instability
Permissive effect	Facilitates the response of the tissues to humoral and neural influences, such as that of the catecholamines, during trauma and extreme stress

Adrenal Cortical Insufficiency

There are two forms of adrenal insufficiency: primary and secondary. Primary adrenal insufficiency, or Addison's disease, is caused by destruction of the adrenal gland. Secondary adrenal insufficiency results from a disorder of the HPA system.

Primary Adrenal Cortical Insufficiency

In 1855, Thomas Addison, an English physician, provided the first detailed clinical description of primary adrenal insufficiency, now called *Addison's disease*. The use of this term is reserved for primary adrenal insufficiency in which adrenal cortical hormones are deficient and ACTH levels are elevated because of lack of feedback inhibition.[28–30]

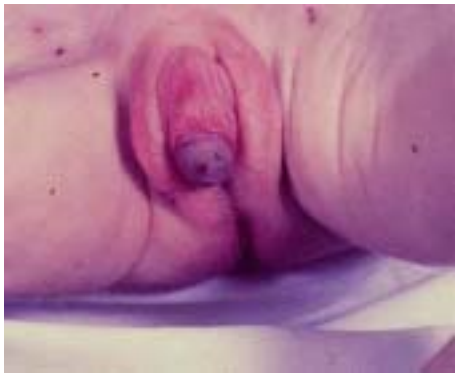


FIGURE 31-15 A female infant with congenital adrenal hyperplasia demonstrating virilization of the genitalia with hypertrophy of the clitoris and partial fusion of labioscrotal folds. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1186]. Philadelphia: Lippincott Williams & Wilkins)

Addison's disease is a relatively rare disorder in which all the layers of the adrenal cortex are destroyed. Autoimmune destruction is the most common cause of Addison's disease in the United States. Before 1950, tuberculosis was the major cause of Addison's disease in the United States, and it continues to be a major cause of the disease in countries where it is more prevalent. Rare causes include metastatic carcinoma, fungal infection (particularly histoplasmosis), cytomegalovirus infection, amyloid disease, and hemochromatosis. Bilateral adrenal hemorrhage may occur in persons taking anticoagulants, during open heart surgery, and during birth or major trauma. Adrenal insufficiency can be caused by acquired immunodeficiency syndrome (AIDS), in which the adrenal gland is destroyed by a variety of opportunistic infectious agents.

Addison's disease, like type 1 diabetes mellitus, is a chronic metabolic disorder that requires lifetime hormone replacement therapy. The adrenal cortex has a large reserve capacity, and the manifestations of adrenal insufficiency usually do not become apparent until approximately 90% of the gland has been destroyed. These manifestations are related primarily to mineralocorticoid deficiency, glucocorticoid deficiency, and hyperpigmentation resulting from elevated ACTH levels. Although lack of the adrenal androgens (*i.e.*, DHEAS) exerts few effects in men because the testes produce these hormones, women have sparse axillary and pubic hair.[31]

Mineralocorticoid deficiency causes increased urinary losses of sodium, chloride, and water, along with decreased excretion of potassium. The result is hyponatremia, loss of extracellular fluid, decreased cardiac output, and hyperkalemia. There may be an abnormal appetite for salt. Orthostatic hypotension is common. Dehydration, weakness, and fatigue are common early symptoms. If loss of sodium and water is extreme, cardiovascular collapse and shock ensue. Because of a lack of glucocorticoids, the person with Addison's disease has

poor tolerance to stress. This deficiency causes hypoglycemia, lethargy, weakness, fever, and gastrointestinal symptoms, such as anorexia, nausea, vomiting, and weight loss.

Hyperpigmentation results from elevated levels of ACTH. The skin looks bronzed or suntanned in exposed and unexposed areas, and the normal creases and pressure points tend to become especially dark. The gums and oral mucous membranes may become bluish-black. The amino acid sequence of ACTH is strikingly similar to that of melanocyte-stimulating hormone; hyperpigmentation occurs in more than 90% of persons with Addison's disease and is helpful in distinguishing the primary and secondary forms of adrenal insufficiency.

The daily regulation of the chronic phase of Addison's disease usually is accomplished with oral replacement therapy, with higher doses being given during periods of stress. The pharmacologic agent that is used should have both glucocorticoid and mineralocorticoid activity. Mineralocorticoids are needed only in primary adrenal insufficiency. Hydrocortisone usually is the drug of choice. In mild cases, hydrocortisone alone may be adequate. Fludrocortisone (a mineralocorticoid) is used for persons who do not obtain a sufficient salt-retaining effect from hydrocortisone. DHEAS replacement also may be helpful in the female patient.

Because persons with the disorder are likely to have episodes of hyponatremia and hypoglycemia, they need to have a regular schedule for meals and exercise. Persons with Addison's disease also have limited ability to respond to infections, trauma, and other stresses. Such situations require immediate medical attention and treatment. All persons with Addison's disease should be advised to wear a medical alert bracelet or medal.

Secondary Adrenal Cortical Insufficiency

Secondary adrenal insufficiency can occur as the result of hypopituitarism or because the pituitary gland has been surgically removed. Tertiary adrenal insufficiency results from a hypothalamic defect. However, a far more common cause than either of these is the rapid withdrawal of glucocorticoids that have been administered therapeutically. These drugs suppress the HPA system, with resulting adrenal cortical atrophy and loss of cortisol production. This suppression continues long after drug therapy has been discontinued and can be critical during periods of stress or when surgery is performed.

Acute Adrenal Crisis

Acute adrenal crisis is a life-threatening situation. If Addison's disease is the underlying problem, exposure to even a minor illness or stress can precipitate nausea, vomiting, muscular weakness, hypotension, dehydration, and vascular collapse. The onset of adrenal crisis may be sudden, or it may progress during a period of several days. The symptoms may occur suddenly in children with salt-losing forms of the adrenogenital syndrome. Massive bilateral adrenal hemorrhage causes an acute fulminating form of adrenal insufficiency. Hemorrhage can be caused by meningococcal septicemia (*i.e.*, Waterhouse-Friderichsen syndrome), adrenal trauma, anticoagulant therapy, adrenal vein thrombosis, or adrenal metastases.

Acute adrenal insufficiency is treated with intravenous fluids and corticosteroid replacement therapy. Corticosteroid replacement is accomplished through the intravenous administration of either dexamethasone or hydrocortisone.

Glucocorticoid Hormone Excess (Cushing's Syndrome)

The term *Cushing's syndrome* refers to the manifestations of hypercortisolism from any cause. Three important forms of Cushing's syndrome result from excess glucocorticoid production by the body. One is a pituitary form, which results from excessive production of ACTH by a tumor of the pituitary gland. This form of the disease was the one originally described by Cushing; therefore, it is called *Cushing's disease*.[32,33] The second form is the adrenal form, caused by a benign or malignant adrenal tumor. The third form is ectopic Cushing's, caused by a nonpituitary ACTH-secreting tumor.[34] Certain extrapituitary malignant tumors such as small cell carcinoma of the lung may secrete ACTH or rarely CRH and produce Cushing's syndrome. Cushing's syndrome also can result from long-term therapy with one of the potent pharmacologic preparations of glucocorticoids; this form is called *iatrogenic Cushing's syndrome*.

The major manifestations of Cushing's syndrome represent an exaggeration of the many actions of cortisol (see Table 31-2). Altered fat metabolism causes a peculiar deposition of fat characterized by a protruding abdomen; subclavicular fat pads or "buffalo hump" on the back; and a round, plethoric "moon face" (Fig. 31-16). There is muscle weakness, and the extremities are thin because of protein breakdown and muscle wasting. In advanced cases, the skin over the forearms and legs becomes thin, having the appearance of parchment. Purple striae, or stretch marks, from stretching of the catabolically weakened skin and subcutaneous tissues are distributed over the breast, thighs, and abdomen. Osteoporosis may develop because of destruction of bone proteins and alterations in calcium metabolism, resulting in back pain, compression fractures of the vertebrae, and rib fractures. As calcium is mobilized from bone, renal calculi may develop.

Derangements in glucose metabolism are found in approximately 75% of patients, with clinically overt diabetes mellitus occurring in approximately 20%. The glucocorticoids possess mineralocorticoid properties; this causes hypokalemia as a result of excessive potassium excretion and hypertension resulting

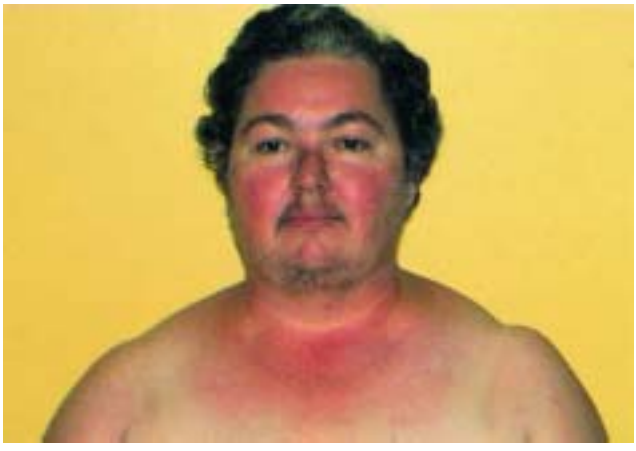


FIGURE 31-16 Cushing's syndrome. A woman who suffered from a pituitary adenoma that produced ACTH exhibits a moon face, buffalo hump, increased facial hair, and thinning of the scalp hair. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1193]. Philadelphia: Lippincott Williams & Wilkins)

from sodium retention. Inflammatory and immune responses are inhibited, resulting in increased susceptibility to infection. Cortisol increases gastric acid secretion, which may provoke gastric ulceration and bleeding. An accompanying increase in androgen levels causes hirsutism, mild acne, and menstrual irregularities in women. Excess levels of the glucocorticoids may give rise to extreme emotional lability, ranging from mild euphoria and absence of normal fatigue to grossly psychotic behavior.

Diagnosis of Cushing's syndrome depends on the finding of cortisol hypersecretion. The determination of 24-hour excretion of cortisol in urine provides a reliable and practical index of cortisol secretions. One of the prominent features of Cushing's syndrome is loss of the diurnal pattern of cortisol secretion. Cortisol determinations often are made on three blood samples: one taken in the morning, one in late afternoon or early evening, and a third drawn the following morning after a midnight dose of dexamethasone. Measurement of the plasma levels of ACTH, measurement of 24-hour urinary 17-ketosteroids, 17-ketogenic steroids, and 17-hydroxycorticosteroids, and suppression or stimulation tests of the HPA system often are made. MRI or CT scans afford a means for locating adrenal or pituitary tumors.

Untreated, Cushing's syndrome produces serious morbidity and even death. The choice of surgery, irradiation, or pharmacologic treatment is determined largely by the cause of the hypercortisolism. The goal of treatment for Cushing's syndrome is to remove or correct the source of hypercortisolism without causing any permanent pituitary or adrenal damage. Transsphenoidal removal of a pituitary adenoma or a hemihypophysectomy is the preferred method of treatment for Cushing's disease. This allows removal of only the tumor, rather than the entire pituitary gland. After successful removal, the person must receive cortisol replacement therapy for 6 to 12 months or until adrenal function returns. Patients also may receive pituitary radiation therapy, but the full effects of treatment may not be realized for 3 to 12 months. Unilateral or bilateral adrenalectomy may be done in the case of adrenal adenoma. When possible, ectopic ACTH-producing tumors are removed. Pharmacologic agents that block steroid synthesis (*i.e.*, etomidate, mitotane, ketoconazole, metyrapone, and aminoglutethimide) may be used to treat persons with ectopic tumors that cannot be resected. Many of these patients also require *Pneumocystis carinii* pneumonia prophylaxis because of the profound immunosuppression caused by the excessive glucocorticoid.

In summary, the adrenal cortex produces three types of hormones: mineralocorticoids, glucocorticoids, and adrenal sex hormones. The mineralocorticoids along with the renin-angiotensin mechanism contribute to the control of body levels of sodium and potassium. The glucocorticoids have anti-inflammatory actions and aid in regulating glucose, protein, and fat metabolism during periods of stress. These hormones are under the control of the HPA system. The adrenal sex hormones exert little effect on daily control of body function, but they probably contribute to the development of body hair in women. The adrenogenital syndrome describes a genetic defect in the cortisol pathway resulting from a deficiency of one of the enzymes needed for its synthesis. Depending on the enzyme involved, the disorder causes virilization of female infants and, in some instances, fluid and electrolyte disturbances because of impaired mineralocorticoid synthesis.

Chronic adrenal insufficiency (Addison's disease) can be caused by destruction of the adrenal gland or by dysfunction of the HPA system. Adrenal insufficiency requires replacement therapy with cortical hormones. Acute adrenal insufficiency is a life-threatening situation. Cushing's syndrome refers to the manifestations of excessive cortisol levels. This syndrome may be a result of pharmacologic doses of cortisol, a pituitary or adrenal tumor, or an ectopic tumor that produces ACTH. The clinical manifestations of Cushing's syndrome reflect the very high level of cortisol that is present.

REVIEW QUESTIONS

- Use thyroid hormone as an example for describing the etiology of primary, secondary, and tertiary hypothyroidism.
- Differentiate genetic short stature from constitutional short stature.
- State the mechanisms of short stature in hypothyroidism, poorly controlled diabetes mellitus, treatment with adrenal glucocorticosteroid hormones, malnutrition, and psychosocial dwarfism.
- List three causes of tall stature.
- Relate the functions of growth hormone to the manifestations of acromegaly.
- Explain why children with isosexual precocious puberty are tall-statured children but short-statured adults.
- Diagram the hypothalamic-pituitary-thyroid feedback system.
- Relate the functions of thyroid hormone to hypothyroidism and hyperthyroidism.
- Explain how a defect in a single step of corticosteroid hormone synthesis produces the manifestations of the adrenogenital syndrome.
- Relate the functions of the adrenal cortical hormones to Addison's disease (*i.e.*, adrenal insufficiency) and Cushing's syndrome (*i.e.*, cortisol excess).

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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