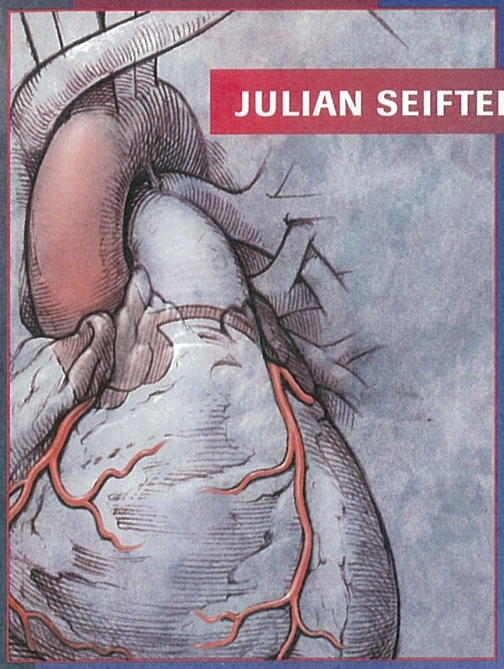
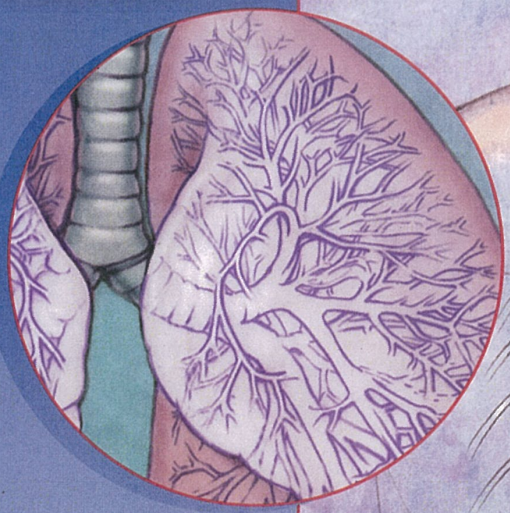
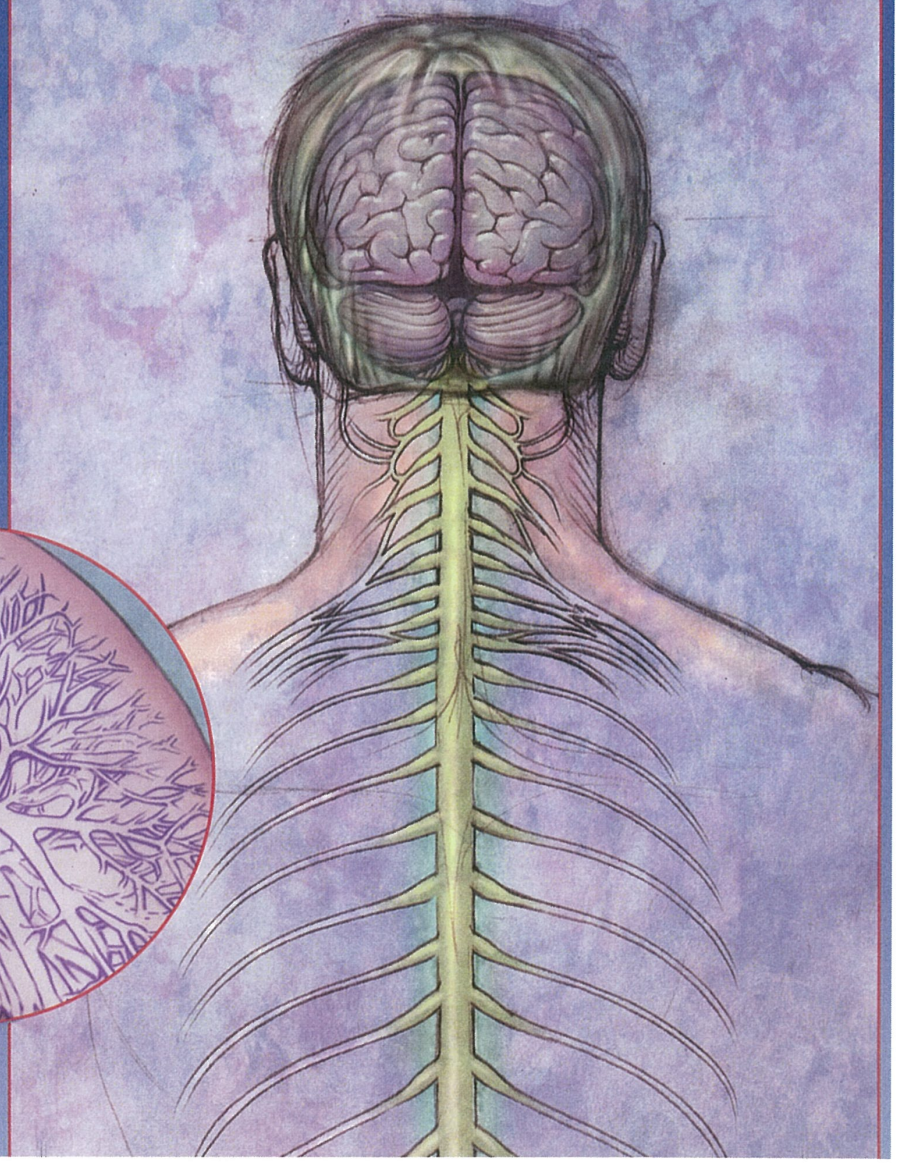
CONCEPTS IN MEDICAL PHYSIOLOGY

JULIAN SEIFTER • AUSTIN RATNER • DAVID SLOANE







LIPPINCOTT WILLIAMS & WILKINS

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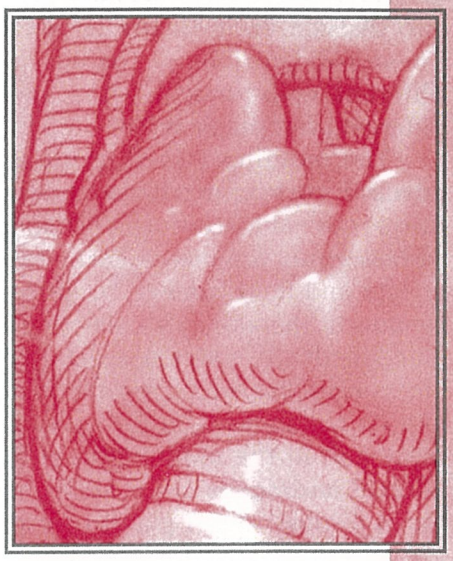
The Adrenal Gland



INTRODUCTION

The **adrenal gland** plays a pivotal role in human endocrine physiology. Although considered one gland anatomically, the adrenal gland functions as two distinct entities: the cortex and the medulla. These two portions of the adrenal originate from different embryonic tissues and have distinctly different physiologic roles.

The outermost shell of the adrenal gland, the **adrenal cortex**, produces three kinds of steroid hormones: aldosterone, cortisol, and androgens. **Aldosterone**, a mineralocorticoid, modulates electrolyte and fluid balance by stimulating sodium retention in the kidney's collecting ducts. **Cortisol**, a glucocorticoid, plays a crucial role in the body's stress response, in the regulation of protein, glucose, and fat metabolism, in the maintenance of vascular tone, and in the modulation of inflammation. The adrenal **androgens** are most important during fetal life as a substrate for placental estrogen production, but they play a minor role during adult life. The **adrenal medulla** is the inner core of the adrenal gland; it produces the catecholamines **epinephrine** and **norepinephrine**, which are also important components of the stress response.

Adrenal function is essential to human life. Adrenalectomy will lead to cardiovascular collapse and death within a few days from a lack of cortisol, which maintains blood vessel tone and blood pressure.

SYSTEM STRUCTURE: ADRENAL ANATOMY AND EMBRYOLOGY

The adrenals are triangular retroperitoneal organs located at the superior poles of the kidneys, lateral to the 11th thoracic and 1st lumbar vertebrae. These glands receive blood from the superior adrenal artery, a branch of the inferior phrenic; the middle adrenal artery, a branch of the aorta; and the inferior adrenal artery, a branch of the renal artery (FIGURE 34.1). This rich blood supply from three distinct locations explains why the adrenals are a frequent site of metastases from distant primary cancers. More importantly, the rich blood supply ensures the adrenals access to the bloodstream to facilitate hormonal secretion. The adrenal arteries anastomose (network) into a subcapsular plexus, which in turn branches into arteries that flow inward. Some of these arteries form capillary networks in the cortex and some form capillary networks in the medulla (FIGURE 34.2). The left adrenal vein drains into the left renal vein, while the right adrenal vein drains directly into the inferior vena cava (IVC). This drainage is analogous to the testicular and ovarian veins. The left testicular/ovarian vein drains into the left renal vein, while the right testicular/ovarian drains right into the IVC.

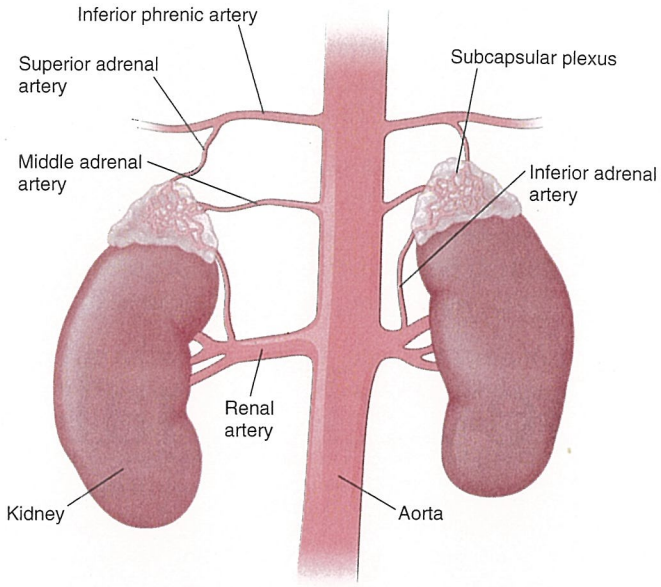


Figure 34.1 Arterial supply to the adrenal glands. The adrenal arteries are not drawn to scale, nor drawn in their exact anatomic locations.

The medulla and cortex of the adrenal glands are separate in structure, function, and embryologic origin. The cortex arises from the mesoderm, while the medulla derives from the ectoderm. The mesodermal gonadal ridge gives rise to the steroidogenic cells of the ovaries and testes as well as the adrenal cortex precursor cells, which migrate to the retroperitoneum. These mesodermal cortical cells are invaded by migrating ectodermal neural crest cells, which will become the medulla. Encapsulation of the adrenal gland around week 8 of fetal life creates a unified organ out of these two originally separate entities.

SYSTEM FUNCTION: THE ADRENAL CORTEX

The adrenal cortex makes up 80% to 90% of the adrenal gland by volume and comprises three histologically and functionally distinct zones, each of which makes a different steroid (FIGURE 34.3). Starting from the outermost, these layers are the **zona glomerulosa,** which produces aldosterone; the **zona fasciculata,** which produces cortisol; and the **zona reticularis,** which produces adrenal androgens, primarily DHEA (dehydroepiandrosterone) and androstenedione. (Some cortisol is produced in the zona reticularis.)

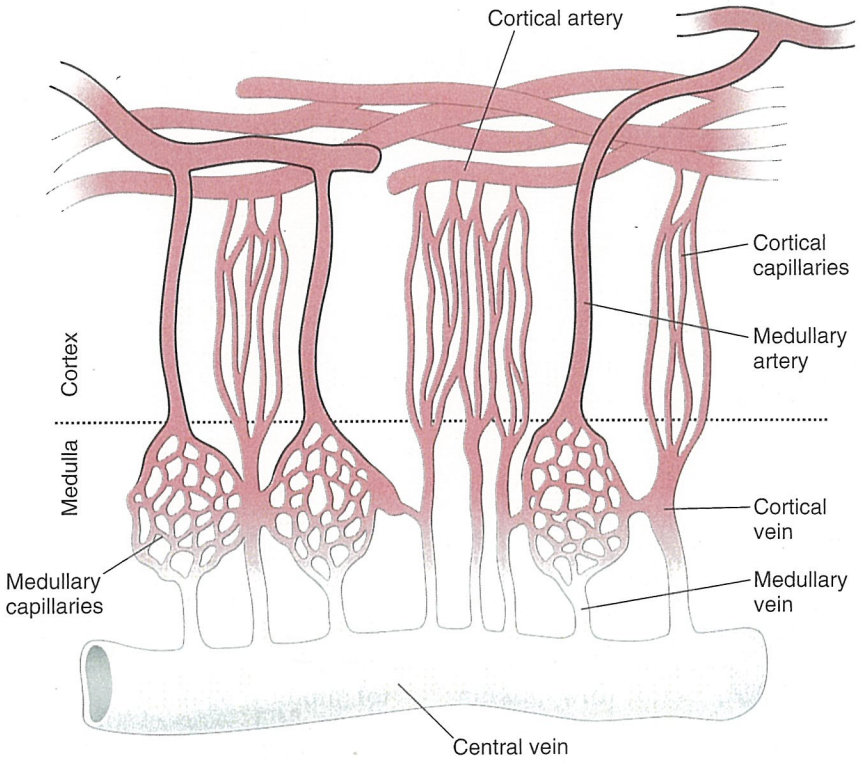


Figure 34.2 Vasculature inside the adrenal glands. The subcapsular plexus gives rise to arteries that form medullary capillary beds and to arteries that form cortical capillary beds.

CRH and ACTH

Production of the steroids in the adrenal cortex is regulated by the **hypothalamic-pituitary-adrenal (HPA) axis** (FIGURE 34.4). At the top of the HPA axis, the hypothalamus releases **corticotropin-releasing hormone (CRH)**, which stimulates the anterior pituitary to release *pro-opiomelanocortin*, a precursor molecule that is cleaved into four main products: *melanocyte-stimulating hormone*, *beta-lipotropins*, *beta-endorphins*, and **adrenocorticotropic hormone (ACTH)**. ACTH, also known as corticotropin, is released into the bloodstream and acts in the cortex, stimulating the synthesis and release of over 50

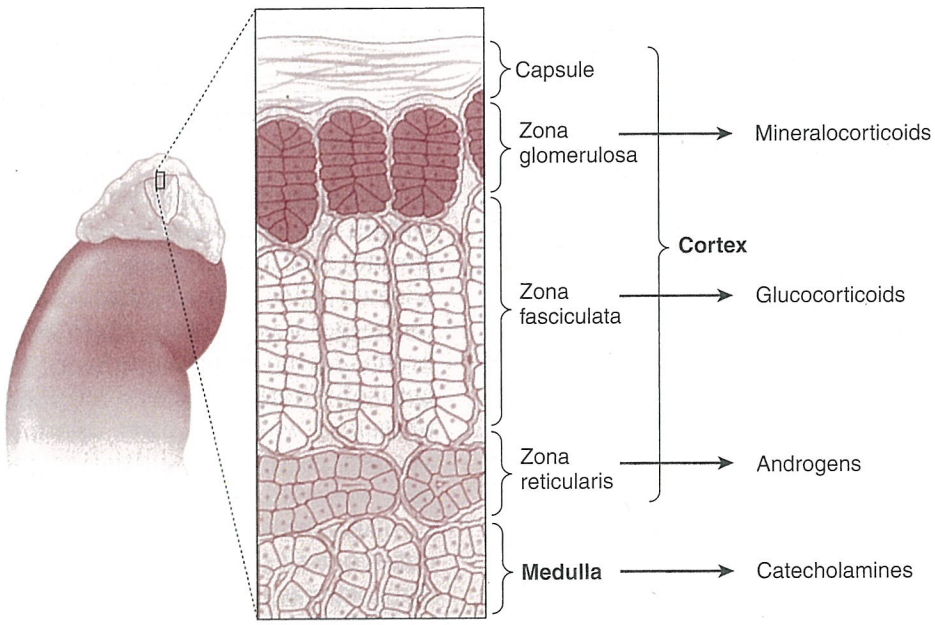


Figure 34.3 Adrenal zonation.

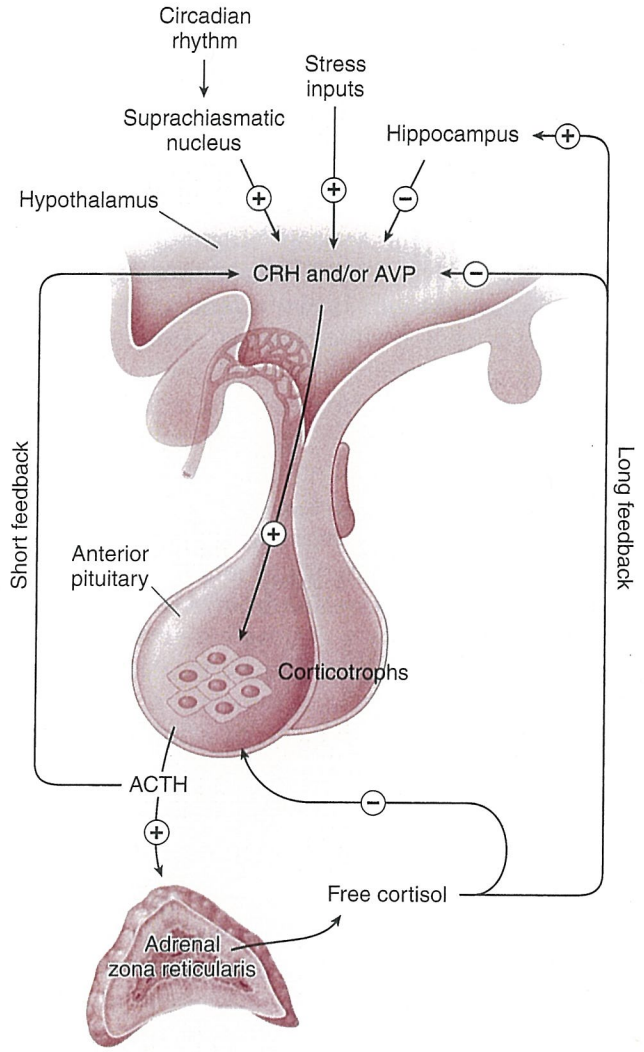


Figure 34.4 Hypothalamic-pituitary-adrenal axis. Stress, circadian rhythms, and negative feedback from cortisol all influence the paraventricular nucleus of the hypothalamus and modulate CRH output. Stressors may be organic in nature (such as hypoglycemia or infection) or psychological.

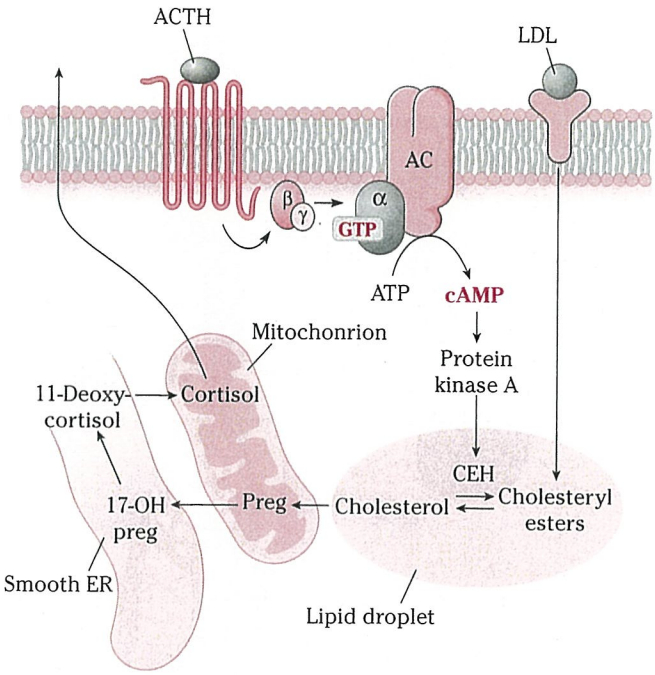


Figure 34.5 Action of ACTH on the adrenal cortex. AC, adenylyl cyclase; CEH, cholesteryl ester hydrolase; G, G protein (linking the receptor to the adenylyl cyclase); LDL, low-density lipoprotein; Preg, pregnenolone (cortisol precursor); R, ACTH receptor; Smooth ER, smooth endoplasmic reticulum.

steroid products, the most important of which are cortisol, the adrenal androgens, and aldosterone, although aldosterone is largely regulated in direct response to serum potassium levels and by *angiotensin II*, a hormone that helps to regulate blood pressure. In a classic endocrine feedback loop, cortisol directly inhibits both CRH production at the hypothalamic level and ACTH at the pituitary level, thereby acting as the main control mechanism for all adrenal cortical hormone production, with the exception of aldosterone.

The cortex responds dramatically to stimulation from ACTH, which elevates steroid production within minutes. It does so by activating a receptor on the cortical cell membranes that is linked to a G protein (FIGURE 34.5). The G protein, in turn, activates adenylyl cyclase and raises the cAMP level, activating a protein kinase. The kinase phosphorylates and hence activates the enzyme **cholesteryl ester hydrolase (CEH)**, which promotes the conversion of cholesteryl esters into free cholesterol. The free cholesterol then supplies the steroid synthesis pathways, as described below. Chronic stimulation with excessive ACTH causes bilateral adrenal hypertrophy, while removal or destruction of the pituitary, which is responsible for producing ACTH, conversely leads to adrenal atrophy.

Cortical Hormones: Their Actions and Regulation

As steroids, the cortical hormones all share certain functional features. They are all secreted into the adrenal blood vessels and circulate from the adrenal veins to target tissues all over the body. At the target tissues, they dissolve into the lipid membranes of the tissues and pass into the intracellular cytosol. There, the steroids bind cytosolic receptor proteins, which in turn bind to particular DNA sequences, thereby initiating the transcription of mRNA, resulting in the synthesis of new proteins.

As mentioned above and described in more detail below, the secretion of steroid hormones from the cortex is regulated by various kinds of negative-feedback loops. TABLE 34.1 summarizes the actions of the cortical steroids.

Table 34.1 ACTIONS OF THE CORTICAL STEROIDS

Adrenal Hormone	Main Actions
Aldosterone	• Increases salt and water reabsorption from kidney tubules • Increases K^+ secretion in kidneys
Cortisol	• Counterregulatory effects: increases blood sugar, increases catabolism of triglyceride and protein • Anti-inflammatory/immunosuppressant effects • Maintains blood vessel tone and hence blood pressure
Androgens	• Help determine male sex characteristics during fetal development and puberty

Aldosterone Action Aldosterone plays a key role in the regulation of fluid balance by enhancing the ability of kidney tubules to absorb salt and water in two ways. First, aldosterone directly stimulates the production and activity of Na^+/K^+-ATPase pumps located in the basolateral side of the cortical collecting ducts. These pumps exchange sodium for potassium, and aldosterone stimulation of these pumps leads to increased sodium reabsorption in exchange for potassium excretion. Remember that increased reabsorption of sodium leads to passive water reabsorption and increased extracellular fluid volume (see Chapter 22).

Second, aldosterone increases salt and water reabsorption in the kidney by creating more apical Na^+ channels, directly increasing sodium permeability on the luminal side of the cortical collecting ducts. Aldosterone also drives K^+ secretion through its effects on the translocation of Na^+. Increased Na^+ reabsorption creates tubular electronegativity and drives paracellular K^+ secretion (see Chapter 24).

Finally, aldosterone acts on the H^+-ATPase in the renal tubule and has other effects on acid-base balance (see Chapter 25). Because it acts on the levels of these inorganic (mineral) electrolytes, it is termed a **mineralocorticoid**.

Aldosterone Regulation Aldosterone regulation is unique in that it is the only adrenal cortical hormone that is secreted largely independently of ACTH. A small amount of ACTH from the pituitary is required for aldosterone release, but aldosterone is regulated mainly by two other control mechanisms: the serum potassium level and the renin-angiotensin-aldosterone (RAA) system. Elevated potassium levels trigger aldosterone secretion, which in turn stimulates renal potassium excretion via the Na^+/K^+ exchange pump to rectify the hyperkalemia. Low blood pressure stimulates the adrenal to secrete aldosterone through the RAA system. This increases salt reabsorption and raises the extracellular fluid volume and blood pressure.

Cortisol Action Cortisol has a multitude of actions, and derivatives of this hormone are used frequently in medical therapy. Cortisol is consequently one of the most challenging adrenal hormones to understand and at the same time one of the most clinically relevant. Cortisol is produced mostly by the fasciculata, with some production in the reticularis. Although mainly exerting glucocorticoid activity (explained below), cortisol also functions as a weak mineralocorticoid, with effects similar to those of aldosterone. Cortisol's precursor, **corticosterone,** also exhibits some glucocorticoid activity. About 20 to 30 mg of cortisol is secreted per day by the adrenals, with 90% to 95% of circulating cortisol bound in the plasma to *cortisol-binding globulin*.

Glucocorticoid action can be thought of mainly in two broad categories: metabolic and anti-inflammatory. Although the myriad metabolic actions of cortisol can be daunting, it is useful to remember that cortisol acts to prepare the body for stress. Teleologically speaking, in times of stress the body does not have the energy surplus to build protein or add to triglyceride and glycogen stores; instead it requires rapidly usable energy for the brain in the form of glucose. Therefore, the body under stress will mobilize amino acids and fatty acids as substrates for gluconeogenesis (see Chapter 31). Under glucocorticoid influence, an increase in all gluconeogenic enzymes raises hepatic gluconeogenesis sixfold. Blood sugar levels climb, while peripheral uptake and utilization of glucose are decreased. To fuel this upregulated gluconeogenic activity, cortisol increases the production of amino acids from muscle breakdown. Synthesis of protein and fat is halted, as the main focus is on survival and the mobilization of stores (catabolism) rather than on growth and repair (anabolism).

This bolus of glucose is liberated from tissue energy stores instead of from the diet. Thus, glucocorticoids are *counterregulatory hormones*, alongside glucagon, epinephrine, and growth hormone. Glucocorticoids reproduce glucagon action and oppose insulin action. However, glucocorticoids do not

INTEGRATED PHYSIOLOGY

The Insulin/Counterregulatory Balance

The stress response induced by cortisol is intended to be only temporary. If exposure to cortisol is prolonged, as in long-term treatment with *prednisone* (a glucocorticoid administered as medicine), the body suffers deleterious effects. A constant elevation of cortisol levels disrupts the normal balance between insulin and cortisol, leaving the body in a prolonged state of catabolism, which can be very destructive.

In *Cushing's disease*, excess ACTH production leads to an abnormal elevation of cortisol and disruption of the metabolic balance. Skin striae, skin thinning, and muscle weakness ensue from excessive protein and collagen breakdown due to cortisol action. In *diabetes mellitus*, low insulin production disrupts the balance between cortisol and insulin. When diabetics experience physical stress such as illness or infection, cortisol levels increase and blood sugar levels increase, and therefore their insulin requirement goes up.

promote glycogen breakdown as does glucagon. This phenomenon is known as glucocorticoid's *glycostatic effect*. (See Integrated Physiology Box *The Insulin/Counterregulatory Balance.*)

Cortisol also has powerful effects on the immune system, which accounts for the widespread use of glucocorticoids as anti-inflammatories and as immunosuppressants. Cortisol reduces the inflammatory response by both blocking the early stages of inflammation and speeding up the resolution of inflammation. Inflammation is decreased in a number of specific ways:

- Stabilization of white cell granules, which release proteolytic enzymes during inflammation
- Decreased capillary permeability (which decreases edema)
- Decreased production of prostaglandins and leukotrienes, both of which are powerful stimuli of inflammation
- Decreased leukocyte migration
- Decreased interleukin-1 (IL-1) and IL-6 release
- Direct suppression of T cells
- Decreased production of lymphocytes and antibodies

Because of the powerful immunosuppressant effects of cortisol, patients taking glucocorticoids for prolonged periods should be considered immunocompromised and at an increased risk for infections.

Cortisol is also a powerful modulator of the allergic response, acting to decrease eosinophil production, increase eosinophil apoptosis, and limit the inflammation that can be deadly in anaphylaxis. Interestingly, cortisol increases red blood cell production in an unknown manner. Finally, cortisol acts to maintain blood pressure by potentiating catecholamines and by directly supporting blood vessel tone.

Cortisol Regulation Cortisol is regulated by the HPA axis, as mentioned above. The median eminence of the hypothalamus is responsible for the production of CRH, which is produced in response to a host of stressful stimuli: trauma, infection, catecholamines, surgery, and so on. How the hypothalamus detects these stimuli has not been completely worked out. CRH is also released in a circadian manner, leading to a diurnal variation with cortisol levels peaking in the early morning. CRH triggers ACTH release from the anterior pituitary. ACTH is also modulated by **antidiuretic hormone (ADH)**, which acts synergistically with CRH to stimulate ACTH release. Cortisol is almost exclusively regulated by ACTH, which activates cholesteryl ester hydrolase (CEH) and ultimately increases the production of *pregnenolone*, a cortisol precursor. Cortisol inhibits CRH and ACTH in a classic negative-feedback loop.

The Androgens The adrenal androgens, like the gonadal androgens, are male sex hormones—that is, they help determine and maintain male sex characteristics. The principal adrenal androgens are **androstenedione**, **dehydroepiandrosterone (DHEA)**, and **DHEA-S**. These hormones have a negligible effect on adult physiology compared to the gonadally produced hormones (such as *testosterone*), which account for the majority of sex hormone effects. They are about one fifth as potent as testosterone. Androstenedione can be converted to testosterone, which is in turn converted to *dihydrotestosterone (DHT)* and *estradiol* in extra-adrenal tissues. These androgens are most important during fetal development and puberty.

In the fetus, the adrenal glands are much larger proportionally than in the adult, and a layer known as the provisional or fetal cortex exists, which is analogous to the adult reticularis. This layer produces DHEA-S, which is converted by the placenta into androgens and estrogens. Overproduction of DHEA-S, as in congenital adrenal hyperplasia (discussed below), can lead to fetal virilization in female infants.

Adrenal androgens are also important during adolescence, when they stimulate the development of pubic and axillary hair in women, which is know as *adrenarche*. Adrenarche and puberty normally coincide, but they are actually two physiologically separate events. Androgen production continues into adulthood and declines with age. Androgens continue to cause groin and axillary hair growth in adult women. Many claims have been made about DHEA as a "youth hormone," but at this point, there is little scientific evidence for the efficacy of DHEA replacement as a fountain of youth.

Steroid Biosynthesis

All the products of the adrenal cortex are steroid hormones, which have a standard four-ring structure and are produced by a similar biosynthetic pathway. Enzymes specific to each layer of the cortex influence the structural differences of the hormones produced. Cholesterol provides the basic four-ring steroid framework. Although the adrenals can synthesize cholesterol de novo from acetyl CoA, 80% of the cholesterol used in adrenal hormone synthesis comes from dietary cholesterol packaged as cholesteryl ester in circulating low-density lipoprotein (LDL) particles. CEH converts the esters to free cholesterol in response to ACTH. The rate-limiting step in hormone biosynthesis is the transfer of cholesterol to the inner mitochondrial membrane of adrenal cells via the *steroidogenic acute regulatory protein (StAR)*, followed by the conversion of cholesterol to pregnenolone. This reaction is catalyzed by the enzyme *desmolase*.

Once pregnenolone is made from cholesterol, the pregnenolone flows downhill through each zone of the cortex, undergoing successive modifications to the basic steroid ring. These modifications result in a distribution of various steroid products throughout the adrenal cortex (FIGURE 34.6). The steroids are released immediately after synthesis; very little of the cortical hormones are stored. This is in direct contrast to the medulla, which packages and stores its products for release under stimulus at a later time.

Some enzymes in the steroid biosynthetic pathways are common to all three zones, while others are unique to a specific adrenal zone. Pregnenolone flows across zones and also undergoes progressive transformation along each zone's unique enzymatic pathway unless an enzyme deficiency in one pathway acts as a roadblock. Such a condition prevents further modification of the steroid product, leading to an excess of premodification substrate that will spill over into the remaining open routes. An example of this hormonal roadblock is found in the pathologic condition **congenital adrenal hyperplasia (CAH)**. (See Clinical Application Box *What Is Congenital Adrenal Hyperplasia?*)

PATHOPHYSIOLOGY: DISEASES OF CORTICAL OVER- AND UNDERPRODUCTION

Levels of cortisol and aldosterone normally vary in response to changing conditions in the body. During stress, cortisol levels rise. When blood pressure is low, aldosterone levels rise. Pathologic conditions, however, may interfere with the adrenal cortex's normal response to stimuli. These conditions are classified as those that cause the overproduction of a hormone and those that cause underproduction. In cases of overproduction, the hormone is secreted at levels out of proportion to adrenal stimuli. In cases of underproduction, the adrenal cortex cannot mount the normal response to stimuli.

Diseases of Overproduction

Diseases of overproduction may be primary to the adrenal gland, or they may originate outside the adrenal (in which case hyperproduction is called secondary). For example, ACTH overproduction in the pituitary can stimulate a perfectly normal adrenal gland to overproduce cortisol. Chronic stimulation of the RAA system due to renal disease can cause a normal adrenal to overproduce aldosterone. Isolated overproduction of androgens is much less common and usually arises from CAH and less commonly from adrenal carcinomas or adenomas.

Hypercortisolism Excess glucocorticoid exposure, called **hypercortisolism**, can lead to a variety of disease manifestations and is one of the most serious adrenal derangements. Excess glucocorticoids may be the result of endogenous overproduction or exogenous administration of glucocorticoid drugs in higher-than-normal amounts. Endogenous cortisol overproduction can be classified into two categories: ACTH-dependent and ACTH-independent. *ACTH-dependent* causes account for 85% of endogenous hypercortisolism and include Cushing's disease (also known as pituitary adenoma), ectopic ACTH production (as occurs with some lung cancers), and ectopic CRH production, which is rare. *ACTH-independent* causes are primary to the adrenal gland. They include adrenal adenoma and adrenocortical carcinoma. Exogenous glucocorti-

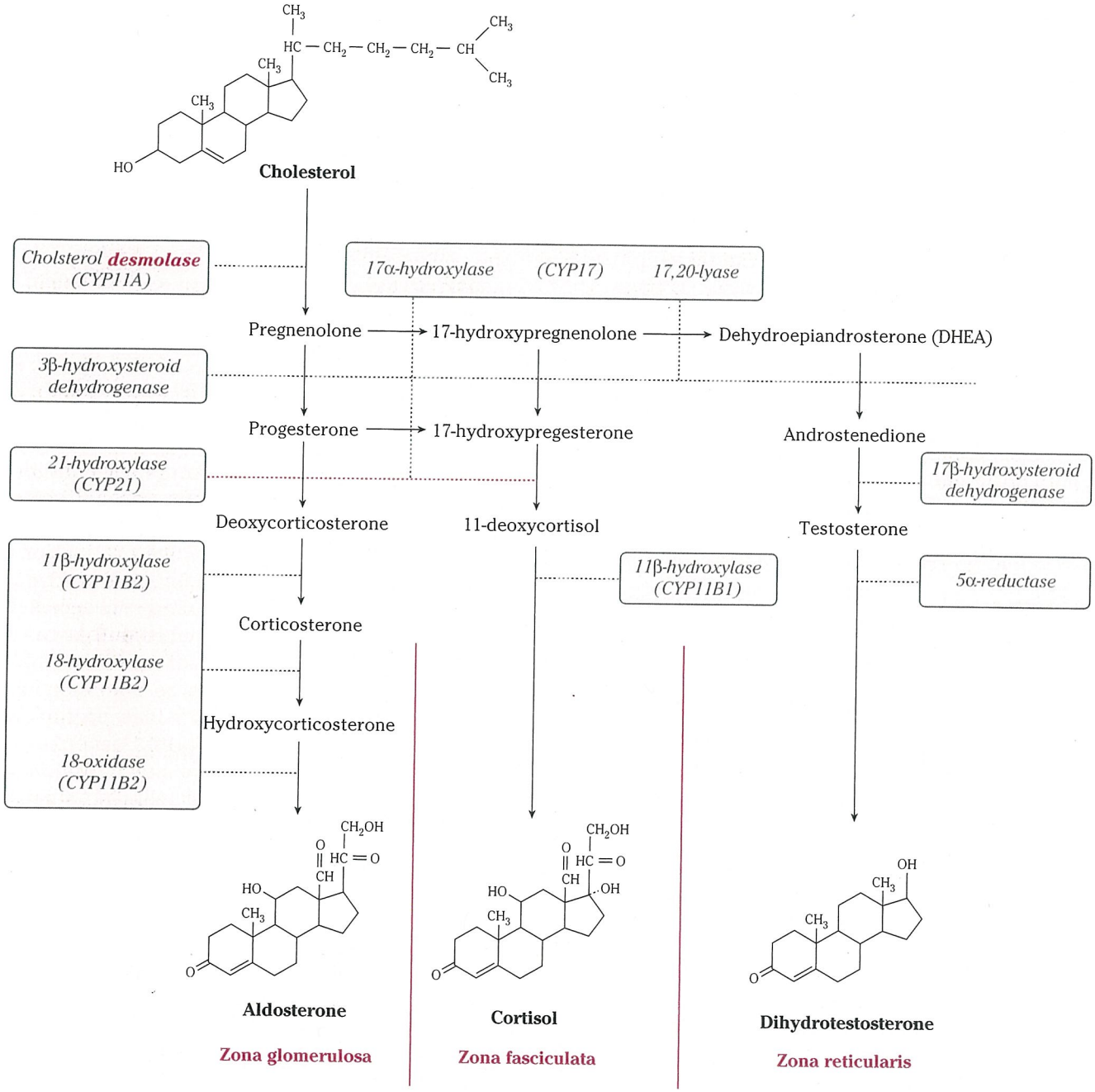


Figure 34.6 Steroid biosynthesis. The line next to 21-hydroxylase is highlighted to indicate the barrier to aldosterone and cortisol synthesis posed by 21-hydroxylase deficiency. Such a barrier causes progesterone and 17-hydroxyprogesterone to build up, which decreases the rate of conversion of pregnenolone to progesterone and of 17-hydroxypregnenolone to 17-hydroxyprogesterone. In turn, pregnenolone and 17-hydroxypregnenolone build up and drive increased DHEA formation.

coids—drug preparations like prednisone or large quantities of steroid inhalers—can also lead to hypercortisolism. Rarely, hypercortisolism is caused by excess secretion of CRH from the hypothalamus.

Hypercortisolism due to any cause yields a constellation of clinical findings known as **Cushing syndrome** (as opposed to Cushing's disease, which is one of many causes of Cushing syndrome). The signs and symptoms of cortisol excess, first described by Harvey Cushing in 1932, include truncal obesity, a round and full face ("moon facies"), a "buffalo hump" of fat on the posterior neck, pigmented skin striae, thinned skin and easy bruising, muscle weakness, osteoporosis, hypertension, and hyperglycemia. The catabolic effects of cortisol cause muscle weakness, osteoporosis, striae, bruising, and hyperglycemia. The abnormal fat distribution is believed to be due to increased lipolysis, which affects the extremities

more than the trunk, but a clear explanation for the moon facies and buffalo hump has yet to be found. Virilizing symptoms of hirsutism and acne can accompany ACTH-dependent hypercortisolism as a result of androgen overproduction from excessive ACTH. Hyperpigmentation is also seen with elevated ACTH levels and is believed to be caused by ACTH cross-reacting with melanocyte-stimulating hormone (MSH) receptors on melanin-producing cells. (See Clinical Application Box *Diagnosing Cushing Syndrome with Lab Tests.*)

Hyperaldosteronism As with hypercortisolism, **hyperaldosteronism** can be classified into two categories: primary (arising from the adrenal) and secondary (extra-adrenal). *Primary hyperaldosteronism*, known as *Conn's syndrome*, arises most often from an aldosterone-producing adrenal adenoma. Hypokalemia, hypernatremia, diastolic hypertension, polyuria, and muscle weakness (secondary to low potassium levels) are characteristics of hyperaldosteronism. Plasma renin levels are low owing to the negative feedback from elevated aldosterone levels.

CLINICAL APPLICATION

WHAT IS CONGENITAL ADRENAL HYPERPLASIA?

A newborn girl in the hospital nursery is discovered to have abnormal findings on examination of her genitals. She has an enlarged clitoris and a single urogenital sinus instead of separate openings for the vagina and urethra. She also has low blood pressure and a high plasma K^+ level. With a putative diagnosis of congenital adrenal hyperplasia, the infant receives hydrocortisone and fludrocortisone (a medicinal mineralocorticoid) and is placed on daily salt supplements. The family is referred to a surgeon and a psychiatrist for consultation.

Patients with **congenital adrenal hyperplasia (CAH)** have a genetic deficiency of *21-hydroxylase*, an enzyme that transforms progesterone to corticosterone in the glomerulosa and transforms *17-hydroxyprogesterone* to cortisol in the fasciculata. When this enzyme is absent, the aldosterone and cortisol precursors encounter a "block" and accumulate. Encountering this backup, progesterone and 17-hydroxy progesterone can overflow into the androgen biosynthetic pathway, where they are converted by *17, 20-lyase* into DHEA and androstenedione, creating a surplus of androgenizing hormones (and a deficiency of aldosterone and cortisol, which cannot be made without 21-hydroxylase). Because of the lack of cortisol, which normally provides negative feedback to the brain, the hypothalamus and pituitary continue to churn out CRH and ACTH to make up for the cortisol deficit, leading to adrenal hypertrophy and even more pregnenolone production.

Excess pregnenolone in the context of 21-hydroxylase deficiency results in more DHEA production. Normally, DHEA has only a minor effect on females, as a stimulus for pubic and axillary hair growth and as a substrate for testosterone production. However, in female fetuses undergoing sexual differentiation, large amounts of DHEA result in clinically significant levels of testosterone, which in turn can lead to virilized external genitalia. At birth, female infants with CAH may be mistaken for male or may have what is known as *ambiguous genitalia*. Male infants with CAH initially may go undiagnosed as they do not have ambiguous genitalia. (They are exposed to virilizing testosterone in utero as part of normal genital development.)

A lack of cortisol and aldosterone can be disastrous for both male and female infants. Aldosterone deficiency in many cases leads to a *salt-wasting crisis* with profound hyponatremia, hyperkalemia, hypotension, and acidosis. Lack of cortisol impairs carbohydrate metabolism and can lead to death from loss of blood vessel tone and blood pressure normally maintained by cortisol.

Glucocorticoid administration makes up for cortisol deficiency and suppresses ACTH, thereby decreasing excess pregnenolone and hence androgen production. Mineralocorticoid and salt administration counteract the salt wasting due to aldosterone deficiency, which is present in the majority of cases. Now that the genetic basis of CAH has been clearly elucidated, prenatal diagnosis and even treatment are possible.

CLINICAL APPLICATION

DIAGNOSING CUSHING SYNDROME WITH LAB TESTS

Several tests are available to help diagnose **Cushing syndrome**, each with varying degrees of sensitivity and specificity. The first and most direct test is measurement of the plasma cortisol level, which is done at night. Normally, circadian rhythms dictate a drop in cortisol secretion during the night. However, because night-time depression in cortisol levels does not occur to the same extent in patients with Cushing syndrome, their late-night plasma cortisol levels may be elevated. A salivary cortisol test has also been recently introduced to assess night-time cortisol secretion. In addition, because increased plasma cortisol leads to increased renal cortisol filtration and excretion, Cushing syndrome can be detected with a 24-hour collection of urine-free cortisol.

The *dexamethasone-suppression test* is used to detect ACTH-dependent causes of Cushing syndrome. The test entails the administration of dexamethasone, followed by measurement of ACTH levels. Dexamethasone is a glucocorticoid and normally suppresses ACTH secretion just as cortisol does. However, ACTH-secreting pituitary adenomas or ectopic sources of ACTH do not respond to negative feedback normally but continue to secrete ACTH even in the presence of increased cortisol levels. (This, indeed, is the pathologic reason for the hypercortisolism in the first place.) Therefore, a failure to suppress the ACTH level upon dexamethasone-suppression testing is indicative of an ACTH-dependent cause of hypercortisolism. Imaging studies can then help locate the tumor that might be secreting ACTH. The sensitivity and specificity of this test, however, are not ideal.

Diagnosis is made by demonstrating a failure to suppress aldosterone production after intravenous saline loading.

The hypertension seen in primary hyperaldosteronism is typically mild, due in part to the phenomenon of *aldosterone escape* (also called mineralocorticoid escape). Because primary hyperaldosteronism affects only one of several renal modes of control over the extracellular fluid volume, the kidney can compensate through its other modes of volume control. The unregulated aldosterone secretion increases salt reabsorption in the distal tubule, leading to increased water reabsorption and increased fluid volume; however, other renal mechanisms respond to the increase in circulatory volume and pressure by reducing salt reabsorption and promoting diuresis. Decreased expression of distal NaCl cotransporters may also contribute to aldosterone escape.

Secondary hyperaldosteronism results from activation of the RAA system via a primary overproduction of renin or a primary kidney disorder involving decreased renal perfusion, such as renal artery stenosis.

Diseases of Underproduction

In 1849, Thomas Addison described the classic features of *adrenal insufficiency*. Six years later he summarized those features: "The leading and characteristic features of the morbid state to which I would direct attention, are, anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connexion with a diseased condition of the supra-renal capsules (*On the constitutional and local effects of disease of the suprarenal capsules*, 1855).

Like hyperaldosteronism, adrenal insufficiency can be categorized as primary (disease originating in the adrenal gland) and secondary (disease originating outside the adrenal). **Primary adrenal insufficiency**, or *Addison's disease*, is characterized typically by both aldosterone and cortisol deficiency. It is caused by adrenal cortex destruction, most often owing to *autoimmune adrenalitis* mediated by lymphocytic attack, but also arising from a host of other causes. Adrenal hemorrhage, tuberculosis, cytomegalovirus (CMV) infection, certain medications, metastases, HIV infection, and rare familial disorders such as adrenal leukodystrophy may all cause destruction of the adrenal cortex. (The medulla is generally spared.)

One case of primary adrenal insufficiency *not* caused by cortical destruction is a genetic deficiency of synthetic enzymes—most commonly deficiency of 21 hydroxylase, as seen in CAH. CAH can lead to an underproduction of cortisol and aldosterone, with concurrent overproduction of adrenal androgens.

Because primary adrenal insufficiency is most commonly caused by destruction of the entire adrenal cortex, glucocorticoid, mineralocorticoid, and

androgen production can all be affected at once. Cortisol deficiency leads to fatigue, weakness, anorexia, weight loss, hypotension, and hypoglycemia. If aldosterone is deficient, hyperkalemia and salt craving may be present as well. Because androgens have little effect on adults, symptoms of androgen deficiency are limited to decreased hair growth in women. The lack of cortisol feedback on the pituitary leads to increased ACTH production, which can be detected serologically or upon dermatologic examination, which reveals ACTH-related hyperpigmentation. *Cortrosyn*, an ACTH analog, can also be used to challenge the adrenals and test for primary adrenal insufficiency.

Primary adrenal insufficiency may present initially as an acute *Addisonian crisis*. This occurs when a patient with underlying undiagnosed adrenal disease encounters a stressor such as surgery or infection and cannot mount an appropriate cortisol response. The crisis is characterized by anorexia, nausea, vomiting, abdominal pain, hyponatremia, and hyperkalemia. Addisonian crises can be fatal if not rapidly treated with cortisol replacement, fluids, and glucose.

Secondary adrenal insufficiency arises from pituitary ACTH deficiency and usually results in a lack of cortisol only, as aldosterone production does not rely on ACTH. There are two main causes of ACTH deficiency. The less common cause is pituitary damage resulting from necrosis, nonfunctioning adenoma, or head trauma. The more common cause is the suppression of a pituitary production of ACTH owing to long-term use of exogenous glucocorticoids, which exert negative feedback on the pituitary. When a patient is treated with steroids, it can take some time for the pituitary to recover fully after the steroids have been stopped. Patients on high-dose or chronic steroids should always be tapered off the drugs to allow for adequate recovery of pituitary function. Similarly, patients taking glucocorticoids chronically, which causes suppression of their HPA axes, may often require "stress-dose steroids"—an increased amount of exogenous corticosteroids when undergoing surgery, trauma, or major illness—to mimic the physiologic response to stress. Such patients require stress-dose steroids because the normal pituitary response has been suppressed and they cannot provide themselves with the physiologic boost in steroid secretion.

SYSTEM FUNCTION: THE ADRENAL MEDULLA

At the core of the adrenal glands are the adrenal medullae, which are part of the sympathetic nervous system and are responsible for the production of catecholamines, epinephrine and norepinephrine. Catecholamines are essential modulators of the rapid response to stress, triggering a variety of fight-or-flight responses, including increased heart rate, elevated cardiac output, and increased blood glucose levels. The parenchymal cells of the medulla, known as **chromaffin cells**, are derived from neural crest cells, as are postganglionic sympathetic neurons, which share a similar structure and function. Like postganglionic sympathetic neurons, the medulla is innervated by cholinergic preganglionic sympathetic neurons. Chromaffin cells are widely distributed throughout the body during fetal life, but the majority degenerate after birth, leaving the adrenal medulla as the main locus of chromaffin cells. However, extra-adrenal chromaffin cells may persist in adult life, especially adjacent to the abdominal aorta, in clusters know as *paraganglia*.

In contrast to adrenal cortical cells, which do not store their products, medullary cells are full of secretory granules, which are storehouses for catecholamines, ATP, opiate-like enkephalins, and proteins called *chromogranins*, which bind to catecholamines. It is believed that two separate types of medullary cells exist, epinephrine-producing and norepinephrine-producing cells. About 80% of the medulla's output is epinephrine.

The Synthesis, Storage, and Release of Catecholamines

Catecholamines are amines with a phenyl ring; they include *dopamine*, *norepinephrine*, and *epinephrine* (FIGURE 34.7). Just as cholesterol is the common precursor of adrenal cortical hormones, tyrosine is the precursor for catechol synthesis. Tyrosine comes from the diet, or it can be synthesized from phenylalanine. Catecholamines are produced in both peripheral and central neural tissues.

Tyrosine hydroxylase is the rate-limiting enzyme and catalyzes the production of dihydroxyphenylalanine (DOPA) from tyrosine. Acetylcholine (ACh), the preganglionic sympathetic neurotransmitter, stimulates both tyrosine hydroxylase activity and synthesis. DOPA is converted to dopamine and then to norepinephrine (NE). At this point, catechol synthesis is cytosolic. NE is then taken up into granules by an ATP-driven monoamine transport or is converted to epinephrine in the cytosol by phenylethanolamine-*N*-methyltransferase (PNMT) and packaged into secretory granules. Both NE and epinephrine are stored in granules until release is triggered. The adrenal medulla is the main producer of epinephrine in the body, while adrenergic axons make mostly NE. The CNS makes dopamine, norepinephrine, and small amounts of epinephrine.

The release of secretory granules occurs by exocytosis of the entire granule contents directly into the extracellular space and circulatory system. ACh

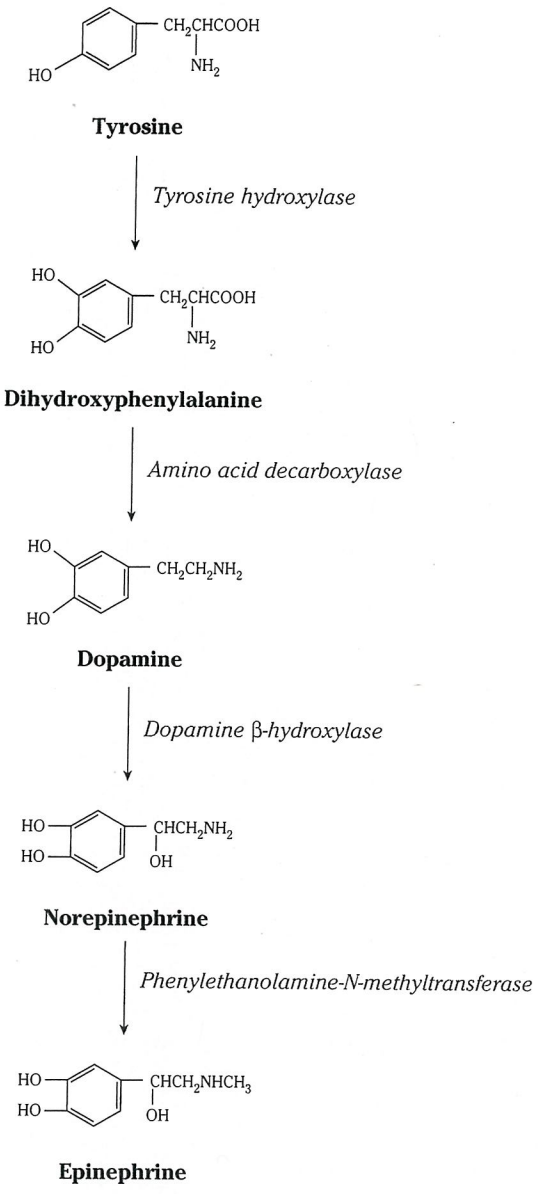


Figure 34.7 Catecholamine biosynthesis. Catecholamines are produced from a tyrosine precursor in the adrenal medulla. This pathway is stimulated by input from the sympathetic nerves.

stimulates voltage-gated calcium channels to open, causing an influx of calcium, which triggers the union of the granule and external plasma membrane. Blood flow to the medulla increases significantly during the secretion of catecholamines, likely as a means of expediting the distribution of the catecholamines to the rest of the body. Vasodilation is controlled neurally and by local vasoactive factors. Once in the bloodstream, NE and epinephrine are active for 10 to 30 s, then exert weaker activity for up to several minutes. Catecholamines are metabolized by two systems, monoamine oxides (MAO), found in nerve endings, and catechol-*O*-methyltransferase (COMT), which is present in many tissues throughout the body. The main product of epinephrine degradation is vanillylmandelic acid (VMA).

Catecholamine Actions and Regulation

Like cortisol, the catecholamines have a wide variety of effects in a great many tissues. They are not steroids, however, and do not bind to cytosolic receptors; they bind to receptors on the surface of target tissues. They are regulated centrally by the nervous system.

Catecholamine Actions Catecholamines have two main types of effect: hemodynamic and metabolic. Hemodynamically, they increase heart rate, cardiac output, blood vessel tone, and extracellular fluid volume (all of which raise the blood pressure). NE and epinephrine both act at adrenergic receptors, of which there are two types, **alpha receptors** and **beta receptors**. NE has greater alpha activity, while epinephrine has an equal effect on alpha and beta receptors. Acting on alpha receptors, NE causes the constriction of blood vessels, which elevates total peripheral resistance and arterial blood pressure. It also stimulates the kidneys to secrete renin, initiating the RAA cascade and leading to tubular salt reabsorption and extracellular fluid volume expansion. Stimulation of β_1 receptors by NE leads to increased cardiac activity; stimulation of β_2 receptors leads to bronchodilation and decreased gastrointestinal motility. Epinephrine has a greater effect on myocardial contractility and heart rate via the β_1 receptors.

Metabolically, NE and epinephrine are counterregulatory hormones like cortisol, opposing insulin action and mimicking glucagon action. Epinephrine is up to 10 times more metabolically active than NE and acts to increase the metabolic rate and stimulate glycogenolysis. Both NE and epinephrine elevate plasma glucose levels by suppressing glucose utilization, increasing glucagon levels, and decreasing insulin production.

Regulation of the Adrenal Medulla Both the postganglionic sympathetic nerve endings and the adrenal medulla release catecholamines in response to signals from the nervous system. The brain registers stress or hypotension (detected by the body's baroreceptors; see Chapter 22) and discharges impulses along the sympathetic nerves. When the sympathetic nerves that innervate the adrenal gland are stimulated, the adrenal medulla releases NE and epinephrine, a sympathetic stimulus that affects the body globally by traveling in the bloodstream. Recall that NE and epinephrine have a short half-life. They do not regulate their own medullary release by

negative feedback as cortisol does. Instead, they are regulated by the central nervous system.

PATHOPHYSIOLOGY: MEDULLARY DYSFUNCTION

As in the adrenal cortex, medullary pathology can be classified as diseases of overproduction and those of underproduction. Once again, these conditions arise because of a dissociation between hormone secretion and the usual stimuli for hormone secretion. In the case of overproduction, unregulated secretion occurs. In the case of underproduction, the adrenal medulla cannot respond to stimuli in the normal manner.

Catecholamine Overproduction

Pheochromocytomas are catecholamine-producing tumors of chromaffin cells, either within the adrenal (90% of cases) or in extra-adrenal chromaffin islands that persist after fetal life. They are rare and are perhaps most remarkable for their overrepresentation as a favorite "zebra" on medical boards. Pheochromocytomas usually produce both NE and epinephrine and are characterized by headache, pallor, palpitations, diaphoresis (sweating), and hypertension. Classically, these symptoms are paroxysmal, but pheochromocytomas may also cause persistent symptoms. Diagnosis is made by collecting a 24-hour urine sample and testing for catecholamines, metanephrines, and VMA.

Catecholamine Underproduction

Isolated adrenal underproduction of catecholamines usually does not lead to any sequelae, as the rest of the sympathetic nervous system can adequately perform the same functions. However, autonomic dysfunction that involves the sympathetic nerves can occur. Autonomic dysfunction may be idiopathic or secondary to diabetes, autoimmune disorders, or central nervous system infections. This dysfunction typically leads to postural hypotension.

Summary

- The two portions of the adrenal gland are the medulla, which secretes catecholamine hormones, epinephrine and norepinephrine, and the cortex, which surrounds the medulla.
- The three layers of the cortex from outermost to innermost are the zona glomerulosa, which secretes the mineralocorticoid aldosterone; the zona fasciculata, which secretes the glucocorticoid cortisol; and the zona reticularis, which secretes adrenal androgens, DHEA, and androstenedione.
- The adrenal glands are very well perfused. The adrenal arteries arise from three separate larger vessels, and when the medulla is stimulated, adrenal blood flow increases far in excess of that needed to meet adrenal oxygen demands. The vascular anatomy and vasodilatory capacity facilitate hormonal secretion.
- The HPA axis regulates adrenal secretion from the cortex. The hypothalamus releases CRH, which stimulates the anterior pituitary to release ACTH.
- ACTH triggers increased CEH conversion of cholesteryl ester to cholesterol, thereby increasing intracellular cholesterol levels. Steroid production from cholesterol, in particular cortisol, increases. Cortisol inhibits the secretion of CRH and ACTH in a classic negative-feedback loop.
- Steroids bind to intracellular receptors and modify DNA transcription.
- Aldosterone increases salt and water reabsorption in the kidney and K^+ secretion in the kidney. Its secretion is regulated primarily by the RAA system (which responds to blood pressure) and the plasma K^+ level.
- Cortisol's major effects are anti-inflammatory, metabolic (as a counterregulatory hormone that mimics glucagon action), and cardiovascular, by potentiating the response to catecholamines and supporting blood vessel tone, thereby helping maintain the blood pressure. Its secretion is regulated by CRH and ACTH. CRH is released in response to physiologic stress and in accordance with circadian rhythms and is suppressed by negative feedback from cortisol.
- The adrenal androgens are physiologically important during fetal development and puberty but are less important and less potent than the gonadal androgens (such as testosterone) during the other periods of life. Adrenal androgen secretion is governed by CRH and ACTH levels.
- All steroids are derived from cholesterol and pregnenolone, a modified form of cholesterol. Cholesteryl esters are delivered to the adrenal by LDLs in the blood and converted to cholesterol by CEH. They are translocated to the inner mitochondrial membrane by the StAR protein and converted to pregnenolone by the enzyme desmolase.

- Enzyme deficiencies can cause roadblocks in the biochemical pathways that lead from pregnenolone to the final end-products cortisol, aldosterone, and the androgens. Such conditions may cut off the production of some end-products and may result in excessive levels of steroid precursors. The precursors may then overflow into parallel biochemical pathways and cause an excess production of other end-products of steroid biosynthesis.
- In the disease congenital adrenal hyperplasia, 21-hydroxylase deficiency causes decreased production of cortisol and aldosterone, an overflow of precursors into the androgen pathways, and excess production of adrenal androgens.
- Hypercortisolism, an overproduction of cortisol, leads to Cushing syndrome. Hypercortisolism may have ACTH-dependent causes, such as pituitary adenoma and ectopic ACTH-secreting tumors, or ACTH-independent causes, such as adrenal tumors or exogenous glucocorticoid administration.
- Hyperaldosteronism may arise from adrenal tumors or kidney disease.
- Destruction of the adrenal glands owing to various causes leads to primary adrenal insufficiency (Addison's disease). Secondary adrenal insufficiency results from decreased ACTH production, whether due to pituitary pathology or the suppression of ACTH by the administration of exogenous glucocorticoids.
- The catecholamines epinephrine and norepinephrine mediate the fight-or-flight response, which includes increased heart rate, elevated cardiac output, and increased blood glucose levels.
- Catecholamines are made from the common amino acid precursor tyrosine.
- Many CNS-processed signals, including stress and hypotension, cause increased sympathetic nervous output, thereby driving the release of adrenal catecholamines.
- Pheochromocytomas are extremely rare catecholamine-secreting tumors of the adrenal medulla. Destruction of the adrenal medulla does not have significant sequelae, since the sympathetic nervous system can compensate for the effects of circulating catecholamines.

Suggested Reading

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REVIEW QUESTIONS

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

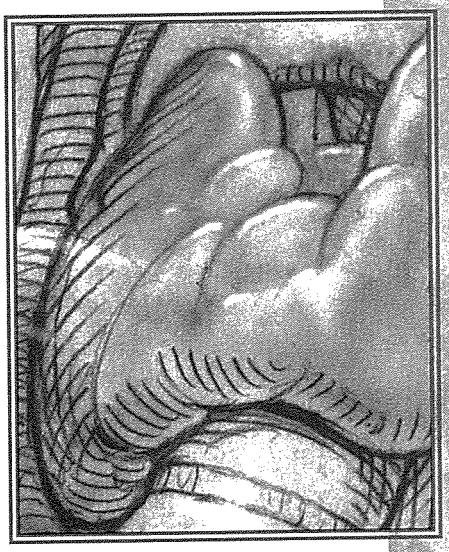
1. A newborn girl is observed to have ambiguous genitalia, low blood pressure, and hyperkalemia and is diagnosed with congenital adrenal hyperplasia. Her 21-hydroxylase deficiency has caused which of the following patterns of adrenal hormone derangement?
   (A) Decreased cortisol, decreased aldosterone, increased adrenal androgens
   (B) Decreased cortisol, increased aldosterone, increased adrenal androgens
   (C) Increased cortisol, decreased aldosterone, decreased adrenal androgens
   (D) Increased cortisol, increased aldosterone, decreased adrenal androgens
   (E) Increased cortisol, decreased aldosterone, increased adrenal androgens

2. A 27-year-old man is treated with oral prednisone (a glucocorticoid) to control a severe asthma exacerbation. After 2 weeks on the medication, his wheezing resolves and he decides to stop taking the prednisone without tapering his doses as prescribed. Two days later, he comes to the emergency room with symptoms of fatigue, weakness, and anorexia. He is hypotensive and hypoglycemic. He probably has adrenal insufficiency because:
   (A) His adrenal cortex is unresponsive to ACTH.
   (B) His ACTH secretion is low due to pituitary dysfunction.
   (C) His ACTH secretion has been suppressed by exogenous glucocorticoids.
   (D) His adrenal glands have been destroyed by lymphocytic infiltration.
   (E) He has an ACTH-secreting pituitary adenoma.
   (F) He has an adrenal adenoma.
   (G) He has an adrenal pheochromocytoma.
   (H) Exogenous glucocorticoids have injured his adrenal glands.

3. A 25-year-old woman with type I diabetes is hospitalized with a severe case of double pneumonia. During her hospital stay, she requires higher-than-usual doses of insulin. This is because:
   (A) Elevated glucagon secretion has increased her plasma glucose level.
   (B) Alveolar inflammation has liberated glucose into the blood.
   (C) Her intake of carbohydrates has increased dramatically.
   (D) Elevated cortisol secretion has increased her plasma glucose level.
   (E) Her adrenal function has been suppressed.

37

The Male Reproductive System



INTRODUCTION

The male reproductive system has three principal functions:

1. The differentiation and maintenance of the primary and secondary sex characteristics under the influence of the hormone testosterone, made in the testes.
2. Spermatogenesis—the creation of the male gametes inside the testes.
3. The penile delivery of sperm from the testes into the female's vagina in the act of procreation. This includes penile erection and ejaculation.

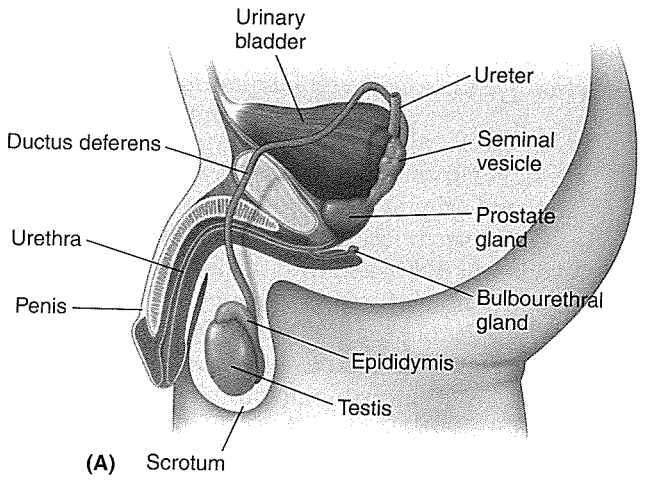
SYSTEM STRUCTURE

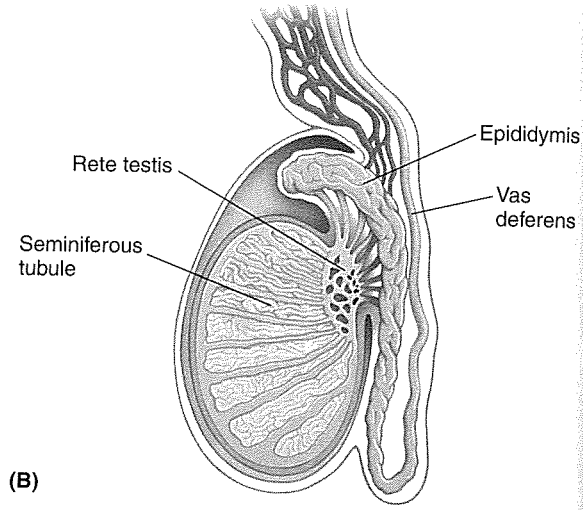
The male reproductive system comprises not only the male genitals, but also the cranial structures that help regulate the performance of the male reproductive system—namely, the hypothalamus and pituitary. At the hypothalamic and pituitary level, however, male and female anatomy and histology are more or less the same. For more details on the hypothalamic and pituitary structures involved in human reproduction, see Chapter 36. In the section that follows, we will focus on the anatomy and histology of the testes, the penis, and the ductal connections between the testes and penis.

The Testes

The male gonads, or **testes**, are suspended from the perineum in an external contractile sac called the **scrotum** (FIGURE 37.1A). Each testis is about 4 cm long, and the testes are perfused by the spermatic arteries. The spermatic arteries are closely apposed with the spermatic venous plexus, and this close contact allows countercurrent heat exchange between artery and vein, cooling the blood that flows to the testes. Countercurrent heat exchange helps keep the testicular temperature cool enough for optimal spermatogenesis (1°C to 2°C cooler than body temperature). The external location of the testes in the scrotum serves as a second important cooling mechanism. Because the testes develop within the abdomen, they descend into the scrotum during fetal life, reaching the deep inguinal rings around week 28 of gestation and inhabiting the scrotum by birth. In some instances (3% of the time in full-term male infants), the testes do not descend—a condition called *cryptorchidism*. Cryptorchidism must be corrected if the male is to have properly functioning, fertile gonads.

The testes are composed of coiled seminiferous tubules embedded in connective tissue (see Figure





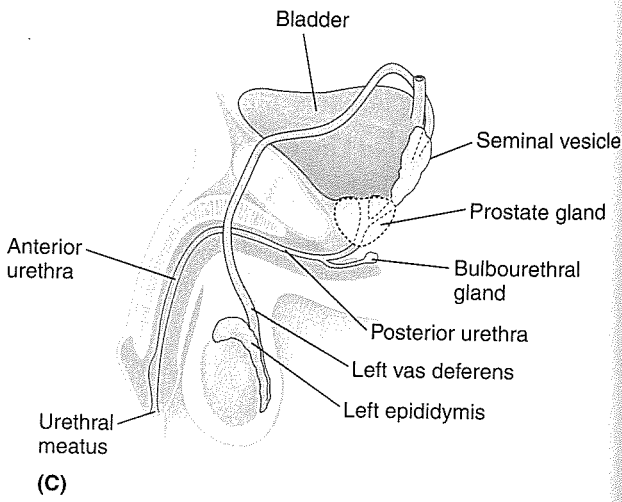


Figure 37.1 Anatomy of the male reproductive system. **A.** Overview. **B.** A closer look at the testis. **C.** The ducts of the reproductive system shown in isolation. The ducts arising from both testes are depicted, converging on the posterior urethra inside the prostate gland.

37.1B). The connective tissue, which makes up about 20% of the testicular mass, contains **Leydig cells**, which make testosterone. The **seminiferous tubules**, constituting 80% of the testicular mass, generate the sperm. The tubules contain two main cell types: spermatogonia and Sertoli cells. **Spermatogonia** are the germ cells that undergo meiosis to give rise to *spermatids*, the immediate precursors to spermatozoa. The copious cytoplasm of the **Sertoli cells** completely envelops and protects the spermatids, sealing them off from any contact with the tubules' outer basement membrane or blood supply. This Sertoli sheath hence forms a **blood-testis barrier** to protect the male gametes from any harmful bloodborne agents, and to prevent the immune system from attacking the unique sperm-specific proteins as though they were foreign antigens. By virtue of their position between the blood and the spermatids, the Sertoli cells also transport nutrients, oxygen, and hormones, such as testosterone, to the spermatids.

The spermatogonia sit outside the blood-testis barrier near the basement membrane. Here, they continuously conduct mitosis. The products of mitosis are pushed toward the tubule lumen and undergo meiosis and differentiation into sperm cells. The Sertoli barrier is fluid and accommodates the passage of cells developing into spermatids. The testes make around 120 million sperm a day. As they differentiate, the sperm migrate into the tubule lumen for transport distally to the *rete testis*, a plexus of ducts that collects sperm from each of roughly 900 seminiferous tubules. The rete testis empties into the **epididymis**, a single coiled tubule running from the top of the testis down its posterior aspect. In the epididymis, sperm are stored and undergo maturation before continuing their voyage outside the testis.

The Ducts and Penis

Each epididymis leads to a long, straight tube called the **vas deferens** (see Figure 37.1C). The vas deferens from the epididymis of each testis rises in the scrotum, ranges laterally through the inguinal canals, runs along the pelvic wall toward the posterior, and descends along the posterior aspect of the bladder. Here the two vas deferens tubes widen into ampullae, which are attached to glands called the **seminal vesicles**. (There are two seminal vesicles, one for each vas deferens.) The seminal vesicles secrete more than half the volume of the semen. The two ampullae each send an ejaculatory duct through the prostate gland, and the ejaculatory ducts join the urethra inside the tissue of the prostate gland. From this point onward, the male urethra serves as part of both the reproductive and urinary tracts, unlike female anatomy, in which the reproductive and urinary tracts are completely separate. Male physiology ensures that micturition and ejaculation do not occur simultaneously.

The urethra next passes through the muscle tissue of the **urogenital diaphragm**, a consciously controllable sphincter. Sitting just under the urogenital diaphragm are the **bulbourethral glands** (also called *Cowper's glands*), which lubricate the urethra with mucus. Finally, the urethra enters the penis. The cylindrical **penis** houses the urethra in erectile tissue, which helps effect the transition between the excretory and reproductive functions of the urethra (FIGURE 37.2). This erectile tissue contains **cavernous sinuses** that fill with blood under circumstances of increased penile blood flow, leading to erection of the penis. When erect, the penis may be inserted into the vagina so that sperm may be delivered to the fallopian tubes.

The erectile tissue is present in three cylinders inside the penis, each called a **corpus cavernosum** and together called the *corpora cavernosa*. Two of the corpora lie dorsally and are sheathed by the *ischiocavernosus muscles*. One lies ventrally and is sheathed by the *bulbospongiosus muscle*. The ventral corpus cavernosum is also called the **corpus spongiosum**, and it is special in that it contains the urethra and forms the *glans penis*, the spongy head of the penis. The corpora are each supplied by a **cavernous artery** that gives out helicine arteries. The penis averages 8.8 cm (3.5 in) in length when flaccid and 12.9 cm (5.1 in) when erect, indicating no correlation between flaccid and erect size.

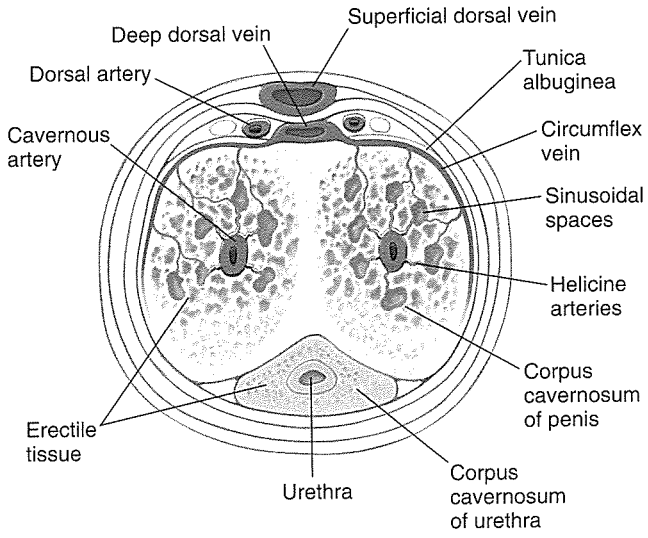


Figure 37.2 Cross section of the penis.

SYSTEM FUNCTION

Just as the female reproductive system is coordinated by the hypothalamus and pituitary, the activities of the male reproductive system are coordinated by the HPG axis, in this case the **hypothalamic-pituitary-testicular (HPT) axis** (FIGURE 37.3). (The gonadal HPT axis is not to be confused with the hypothalamic-pituitary-thyroid axis, also labeled HPT.) The male axis shares with the female the exact same hypothalamic hormone, **gonadotropin-releasing hormone (GnRH)**, and the same pituitary gonadotropins, **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**. (The gonadotropins are named for their female reproductive functions, but they act in the male nonetheless.) The same array of gonadal steroid hormones that is produced by the ovary is also synthesized by the male reproductive system, but in different proportions. Because of differential expression of enzymes in the steroid synthesis pathway, the female gonad makes predominantly progesterone and estrogen, while the male gonad predominantly makes the androgen steroid hormone **testosterone**. Testosterone inhibits the secretion of GnRH, LH, and FSH in a classic negative-feedback loop.

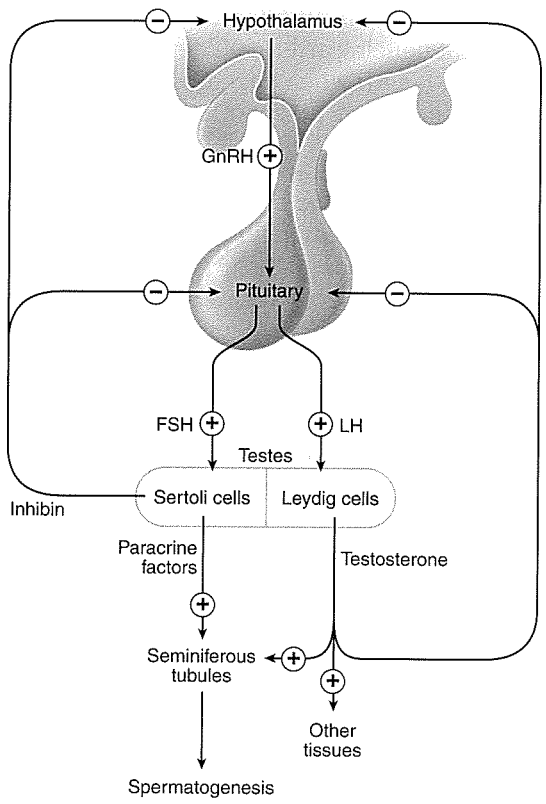


Figure 37.3 Hypothalamic-pituitary-testicular axis. Plus signs represent stimulation; minus signs represent inhibition.

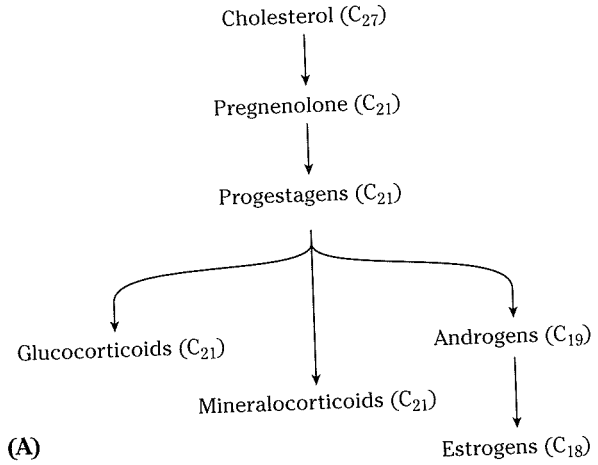
The HPT Axis

GnRH is the initial driver of testicular function. It is secreted in a pulsatile fashion (one pulse every 1 to 3 hours) and distributes to the pituitary gonadotrophs through the hypothalamic-pituitary portal circulation. There, the releasing hormone stimulates the LH- and FSH-secreting cells. Each GnRH pulse directly prompts an LH pulse from the gonadotrophs. More frequent or larger-amplitude GnRH pulses result in more frequent or larger-amplitude LH pulses. GnRH also increases FSH release, but the correlation between GnRH and FSH release is not as exact.

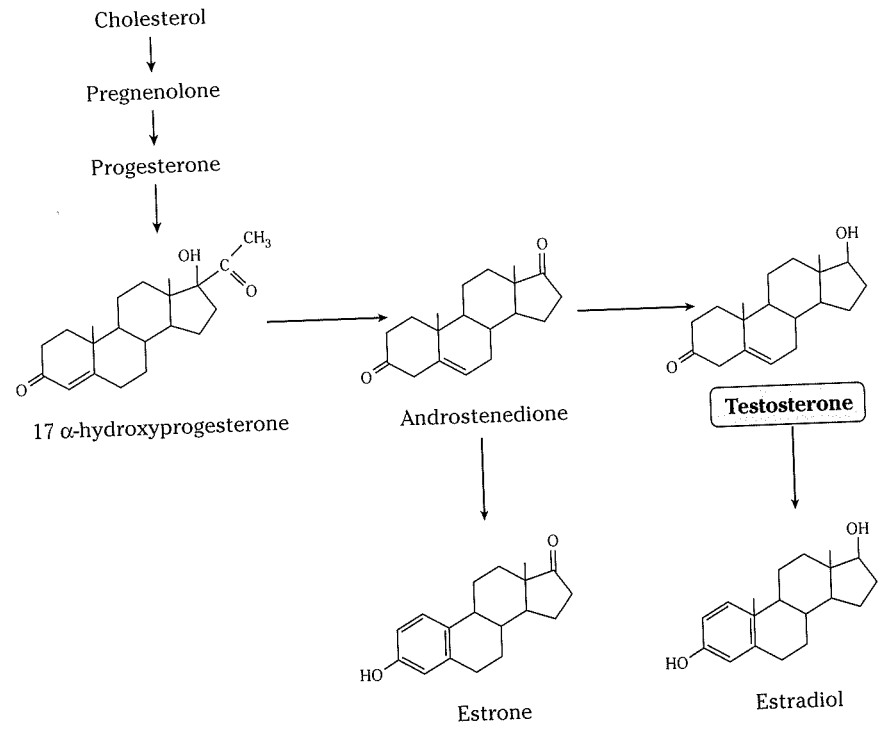
LH acts on the Leydig cells. The LH signal is transduced by a seven- transmembrane receptor linked through a G protein to adenylyl cyclase, which produces cAMP. LH-dependent elevations in cAMP promote testosterone synthesis from cholesterol and promote the growth of Leydig cells. Testosterone synthesis is increased by the activation and increased expression of key proteins involved in steroidogenesis, such as the *steroidogenic acute regulatory protein (StAR)*. StAR shuttles cholesterol into steroid-manufacturing cells. The Leydig cells of the testis are unique in their ability to make testosterone in large amounts (FIGURE 37.4). While the zona reticulata cells of the adrenal gland also make androgens, the adrenal pathway stops at androstenedione, the immediate precursor to testosterone. (Some peripheral tissues can make testosterone from androstenedione in small amounts.)

FSH, meanwhile, binds to receptors on the Sertoli cells, activating the production of proteins involved in spermatogenesis. FSH also stimulates glucose metabolism, thereby providing energy to the sperm precursors. (Spermatogenesis will be discussed in more detail below.) Finally, FSH upregulates the expression of the androgen receptor in Sertoli cells, thereby potentiating the influence of testosterone upon spermatogenesis.

Like all steroids, testosterone binds an intracellular receptor, which binds DNA transcription factors and influences gene expression. The distribution of testosterone receptors in the body tissues determines the targets of testosterone action. In addition, target tissues express an enzyme that converts testosterone to its more active form, **dihydrotestosterone (DHT)**. This enzyme is *5α-reductase*. DHT binds more avidly to the androgen receptor than does testosterone itself. Testosterone from the Leydig cells passes through the Sertoli cells and into the seminiferous tubules, where, alongside FSH, it promotes spermatogenesis. The Sertoli cells make **androgen-binding protein (ABP)**, which helps them to retain testosterone. Testosterone also acts systemically, promoting growth and sustaining gene expression in many peripheral tissues. Testosterone is transported



(A)



(B)

Figure 37.4 Biosynthesis of androgens. **A.** The steroidal family tree. **B.** A closer look at testosterone and its androgen precursors.

in the blood by **sex hormone-binding protein (SHBP)**, also called *sex hormone-binding globulin*, a liver-produced carrier protein that is structurally similar to ABP. It is thought that testosterone and SHBP itself may act at cell membrane receptors, in addition to testosterone's genomic effects. This is parallel to the genomic and nongenomic modes of signal transduction employed by thyroid hormone.

Finally, testosterone inhibits GnRH and gonadotropin secretion. Thus, testosterone limits its own production and action. **Inhibin** from the Sertoli cells also inhibits the pituitary and hypothalamus. Inhibin is a TGF-β glycoprotein hormone. Investigations suggest that additional feedback mechanisms link Sertoli cell behavior with Leydig cell behavior. TABLE 37.1 summarizes the actions of testosterone.

Table 37.1 TESTOSTERONE ACTIONS

Causes and sustains expression of the male sex characteristics:
Embryologic development of male genitals and ducts
Growth of penis, testes, and prostate at puberty
Growth of hair, larynx
Promotion of positive nitrogen balance in muscles, bones, and skin (promotion of increased protein anabolism, requiring retention of more nitrogen-containing amino acids)
Increased libido and aggression
Causes spermatogenesis
Inhibits HPT axis (negative feedback)

The Expression of Male Sex Characteristics

The male reproductive system begins to function during embryonic life. As soon as the testes form and are capable of secreting testosterone, the androgen begins to act on the body tissues. At this stage, the hormone differentiates the fetus into a male with the appropriate *primary sex characteristics*—the male genitals. At puberty, testosterone causes sustained expression of the *secondary sex characteristics*, which are gender-based phenotypes other than the genitals, such as hair growth, muscle development, and a low voice.

Fetal Life and Infancy (Primary Sex Characteristics)

While the testes do act in utero, they cannot act before they have formed, and they do not form right away. In fact, before 6 weeks of gestation, the gonads of genotypically male or female embryos have not begun to differentiate into either ovaries or testes. The so-called "indifferent gonad" has an inner medullary (male) and an outer cortical (female) layer. In addition, the anatomic precursors of both males (the Wolffian ducts) and females (the Müllerian ducts) are present. Only at 6 to 8 weeks of gestation is male sexual development initiated by the *SRY* gene, a gene on the short arm of the Y chromosome. *SRY* encodes a zinc finger DNA-binding protein called *testis determining factor (TDF)*. Under the influence of TDF, the medullae of the indifferent gonads develop while the cortices regress. The previously indifferent gonads differentiate into testes: embryonic germ cells form spermatogonia, coelomic epithelial cells form Sertoli cells (6 to 7 weeks of gestation), and mesenchymal stromal cells form Leydig cells (8 to 9 weeks of gestation).

Now the testes can begin to act. The Sertoli cells secrete a *Müllerian-inhibiting factor (MIF)*, which causes regression of the Müllerian ducts. Human chorionic gonadotropin (hCG)—which is structurally related to LH—stimulates the Leydig cells to proliferate and secrete testosterone. The testosterone is reduced to DHT in target tissues by 5α-reductase. As long as target tissues contain the androgen receptor and 5α-reductase, DHT induces those tissues to form the primary male sex characteristics, the male reproductive organs. Under the influence of DHT, the Wolffian ducts differentiate into the epididymis, vas deferens, and seminal vesicles. The genital tubercle transforms into the glans penis, the urethral folds grow into the penile shaft, and the urogenital sinus becomes the prostate gland. Finally, DHT causes the genital swellings to fuse, forming the scrotum.

At its peak, the fetal testosterone level reaches 400 ng/dL, but by birth it falls below 50 ng/dL. There is a brief spike in the male infant's testosterone level between 4 and 8 weeks after birth, but its function is not well understood. Otherwise, the testosterone level remains low throughout childhood, until puberty.

Puberty and Beyond (Secondary Sex Characteristics)

Puberty is the process by which males and females achieve reproductive capacity, and it begins in both sexes with an increase in hypothalamic GnRH secretion. It is possible that this increase is in response to decreasing hypothalamic sensitivity to testosterone's negative-feedback effects. As the child approaches adolescence, the hypothalamus gradually escapes inhibition and GnRH secretion rises. LH and FSH secretion in turn rise, and testosterone secretion from the testes increases. Gradual maturation of hypothalamic neurons probably plays a role in this pubertal change in GnRH secretion.

Increased testicular production of testosterone and other androgens at puberty has a host of effects. The earliest one is enlargement of the penis and testes. From the beginning to the end of puberty, the testicular volume more than quadruples. Spermatogenesis commences (with testosterone effects perhaps being most important on the spermatids), and the prostate gland is stimulated to grow. Growth occurs in many tissues outside the reproductive system as well.

Androgens are **anabolic steroids**; they promote the storage of energy in complex molecules. While androgens promote protein synthesis, an anabolic hormone like insulin has a greater effect on the formation of complex carbohydrates and fats. Increased protein synthesis is associated with the growth of skeletal muscle, bones, skin, and hair (pubic, axillary, facial, chest, arms, and legs) and the growth of the larynx (which deepens the voice and causes the thyroid cartilage, or Adam's apple, to protrude). Men on average have around 50% more muscle mass than women; they have stronger, denser bone matrices and thicker skin. Muscle does not contain 5α-reductase, so it appears that testosterone, not DHT, promotes muscular

protein anabolism. However, testosterone or DHT may promote muscular anabolism via extramuscular effects, such as the stimulation of growth hormone and insulin-like growth factor (IGF-1) production.

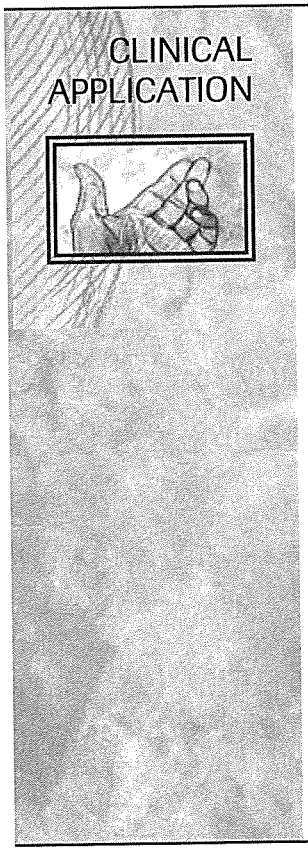
Collectively, the development of the secondary sex characteristics is called **virilization** (after the Latin *vir* for man). It appears that while testosterone promotes all of these effects—genital growth and spermatogenesis, hair growth, behavioral changes, and anabolism in peripheral tissues—certain androgen precursors, metabolic byproducts, and pharmaceutical androgen analogs preferentially serve peripheral anabolism. Many of these metabolites and drugs are abused by bodybuilders and athletes. (See Clinical Application Box *The Use and Abuse of Anabolic Steroids.*)

Testosterone, combined with a genetic predisposition, also influences hair growth on the head. Male-pattern baldness typically begins with a decrease in hair growth on the top of the head and progresses to a complete lack of hair growth extending from the top of the head down. Both factors, the androgens and the genes, are necessary for baldness to occur; a man without the genetic predisposition will not become bald regardless of his testosterone level. A woman with the genetic predisposition will usually not become bald unless she suffers from excess androgen production. Similarly, a castrated male with low testosterone levels will not become bald even if he has a genetic predisposition.

Once testosterone levels rise during puberty, they reach a plateau and remain elevated until a man reaches his seventies, when they begin to decline. This event, called the male *climacteric*, may create some symptoms resembling those of female menopause. However, hormone replacement therapy (HRT) is not commonly used to treat these symptoms. One reason is that men in this age group are at increased risk for prostate cancer. Because testosterone has proliferative effects on the prostate, HRT might further increase the risk of prostate cancer. While testosterone does promote spermatogenesis, this testicular function is remarkably well preserved in men even after the climacteric.

The Haploid Life Cycle in the Male

As mentioned above, spermatogenesis begins with puberty and continues into the eighth decade of life. Spermatogenesis has three phases: **spermatocytogenesis**, during which the primordial spermatogonia divide by mitosis and differentiate into *spermatocytes*; **meiosis**, resulting in four haploid gametes called spermatids, each with a quarter of the cytoplasm of the original spermatogonium (see Chapter 36); and **spermiogenesis**, during which the



THE USE AND ABUSE OF ANABOLIC STEROIDS

Some athletes at amateur and professional levels use regimens of anabolic steroids as a strength and muscle-building strategy despite the fact that such a practice is illegal. The risks of anabolic steroid use include:

- Suppression of the HPT axis by negative feedback on the hypothalamus and pituitary, leading to decreased FSH, LH, and testosterone levels. This leads to gonadal atrophy and impaired spermatogenesis.
- Increased peripheral metabolism of those androgens to estrogens, with feminizing effects such as gynecomastia (breast development in males).
- High cholesterol, high blood pressure, abnormal blood clotting, and other hematologic and cardiovascular risks.
- Irreversible virilization in women.

The effectiveness of anabolic steroids in building muscle has been controversial. However, recent literature has begun to support the notion that anabolic steroids do increase muscle mass in athletes. Older studies generally failed to reproduce the context, duration, and dosage used by competitive athletes.

Anabolic steroids are obtained illegally via the black market. However, "dietary supplements" provide a legal way to obtain some varieties of anabolic steroids. The baseball player Mark McGwire is known to have used an androstenedione-containing dietary supplement during his record-breaking season. While the effects of the supplement on athletic performance are a subject of controversy, data suggest that androstenedione does indeed have harmful cardiovascular effects.

spermatids are nourished and physically reshaped by the surrounding Sertoli cells. The product of spermiogenesis is spermatozoa, or sperm (FIGURE 37.5). After spermiogenesis, the epididymis and reproductive tract glands help prepare the sperm for fertilization.

Spermatocytogenesis and Meiosis The evolving group of cells spanning from spermatogonia to spermatozoa is sometimes called the **spermatogenic series**. Not all spermatogonia enter into the spermatogenic series. If they did, they would be consumed—as happens to the oogonia in the ovary, eventually leading to menopause. Instead, the testis continually replenishes its own supply of spermatogonia. As they undergo mitosis, some of the new ones are committed to the spermatogenic series, while some remain undifferentiated. The undifferentiated stem cells are called **type A spermatogonia**, and the differentiated spermatogonia committed to becoming spermatocytes are called **type B spermatogonia**.

Once this allocation of mitotic products into one group or another occurs, spermatocytogenesis continues as follows. Type A spermatogonia remain on the outside of the blood-testis barrier, while type B spermatogonia cross it, becoming enveloped by the cytoplasmic processes of the Sertoli cells. These type B spermatogonia differentiate further and enlarge to become *primary spermatocytes*. The primary spermatocytes then enter meiosis, a process that takes around 3.5 weeks to complete, almost all of which is spent in prophase (when the newly replicated chromosomes condense). Each primary spermatocyte divides into two *secondary spermatocytes*, which in turn divide again into a total of four haploid spermatids. Each spermatid contains either an X chromosome or a Y chromosome. The male's gamete thus decides the sex of his offspring.

Spermiogenesis Spermiogenesis begins once the spermatids are created and delivered into the embrace of the amoeboid Sertoli cells (FIGURE 37.6). The spermatid elongates and reorganizes its nuclear and cytoplasmic contents into a spermatozoon with a distinct head and tail. The head consists of a condensed nucleus surrounded by a thin layer of cytoplasm. The rest of the retained cytoplasm and cell membrane is shifted toward the opposite end of the sperm, the tail. A large amount of the spermatid's cytoplasm is shed into the surrounding Sertoli cell during spermiogenesis. As the transformed sperm is extruded into the seminiferous tubule lumen, the discarded cytoplasm

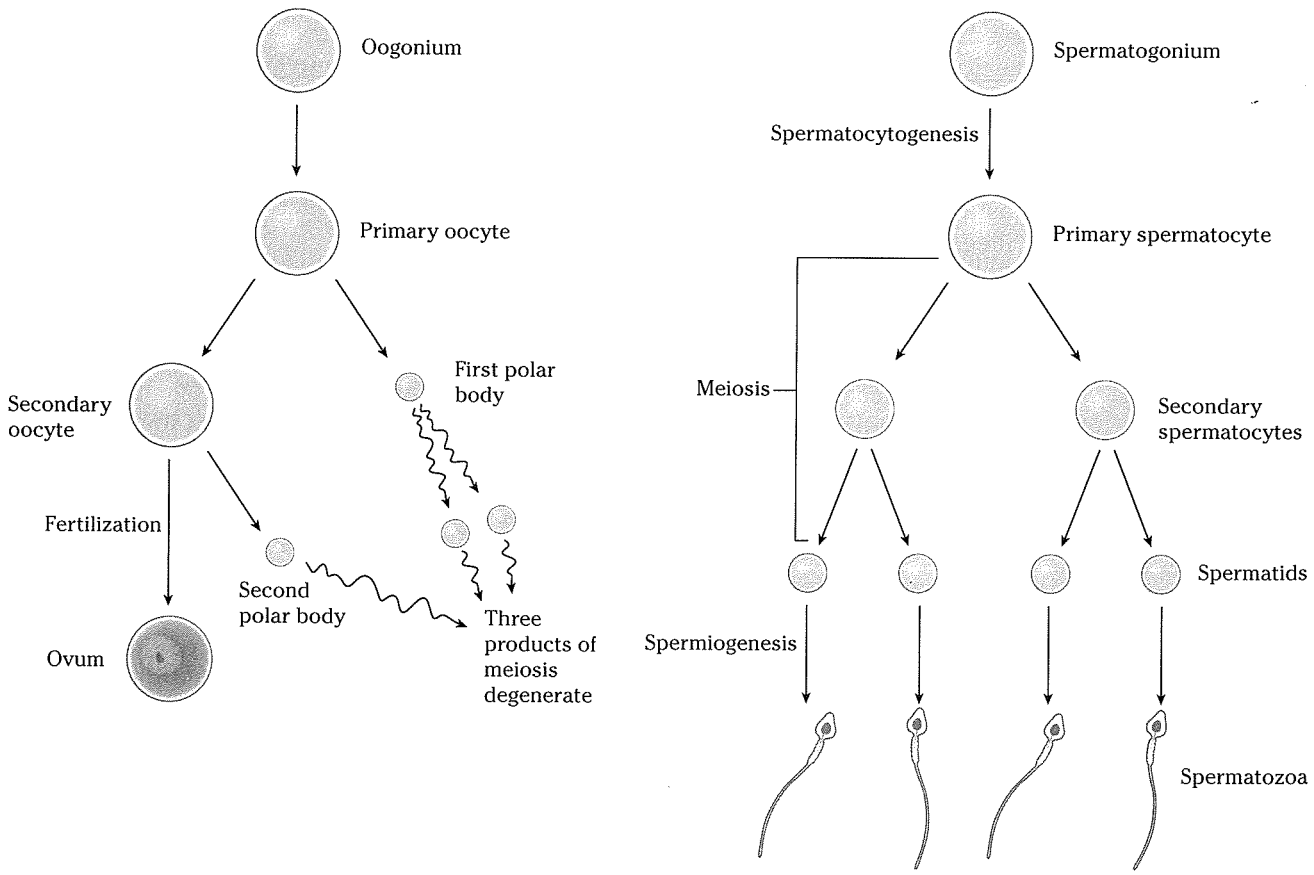


Figure 37.5 Spermatogenesis and oogenesis compared.

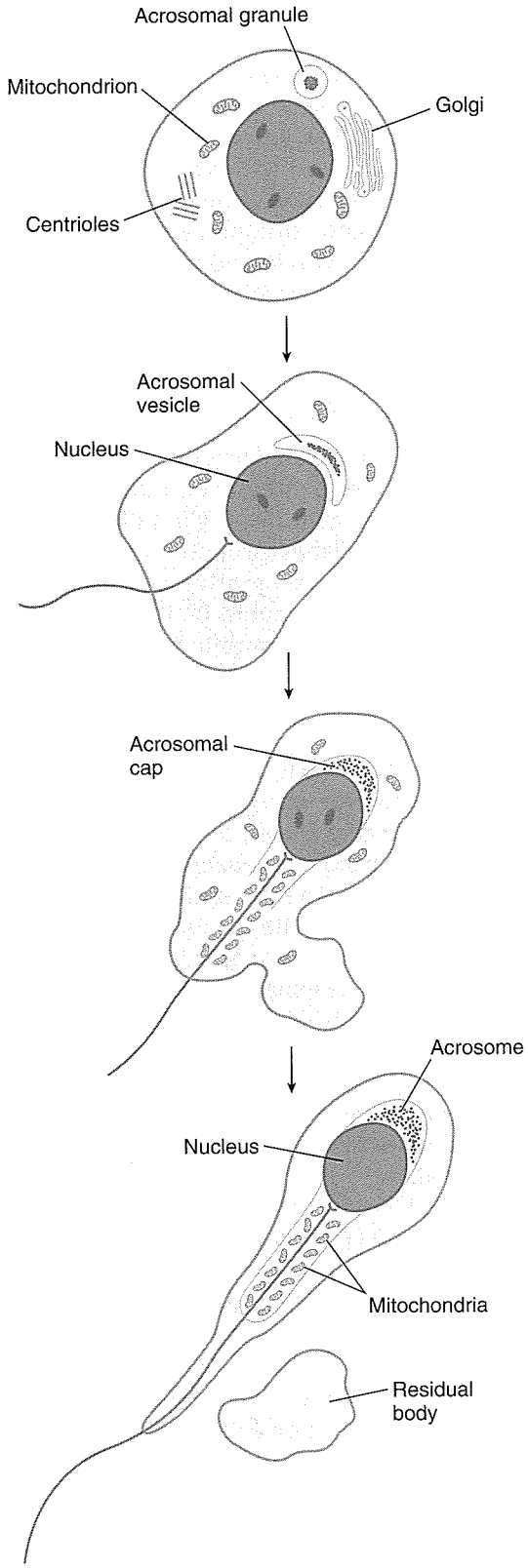


Figure 37.6 Spermiogenesis.

remains embedded in the cytoplasm of the Sertoli cell, where it is ultimately phagocytized.

The structure of sperm cells enables them to swim up the female reproductive tract and fertilize oocytes. The tail of a sperm contains a *flagellum* for motility. Originating from one of the centrioles of the sperm cells, the flagellum consists of a central skeleton of microtubules called the *axoneme*. The axoneme is arranged in the ancient 9 + 2 pattern characteristic of eukaryotic cilia and flagella across all kingdoms and phyla of life: 9 pairs of microtubules surrounding 2 central tubules, linked via a complex array of protein bridges. The sperm cell's mitochondria aggregate along the proximal end of the flagellum and supply energy for movement to the flagellum. The flagellum enables the sperm to swim.

The anterior two thirds of the head of the sperm cell is surrounded by a thick capsule known as the **acrosome**, formed from the Golgi apparatus. The Golgi apparatus contains numerous hydrolytic and proteolytic enzymes, similar to those found in lysosomes, and ultimately facilitates the sperm's penetration of the egg for fertilization. There is also evidence to suggest a role for the acrosomal enzymes in penetrating the mucus of the female cervix.

Epididymal Sperm Maturation and Storage After spermiogenesis is complete, the sperm pass out of the testis (through the rete testis) and into the epididymis, where growth and differentiation continue. After the first 24 hours in the epididymis, the sperm acquire the potential for motility. However, the epithelial cells of the epididymis secrete inhibitory proteins that suppress this potential. Thus, the 120 million sperm produced each day in the seminiferous tubules are stored in the epididymis, as well as in the vas deferens and ampulla. The sperm can remain in these excretory genital ducts in a deeply suppressed and inactive state for over a month without losing their potential fertility.

The epididymis also secretes a special nutrient fluid that is ultimately ejaculated with the sperm and is thought to mature the sperm. This fluid contains hormones, enzymes (such as glycosyltransferases and glycosidases), and nutrients that are essential to achieving fertilization. The precise function of many of these factors is not known, but enzymes like gamma-glutamyl transpeptidase are thought to serve as antioxidants defending against mutations in the sperm.

Potentiation in the Ejaculate The accessory genital glands—the seminal vesicles, prostate gland, and bulbourethral glands—also contribute to potentiation. During ejaculation, their secretions dilute the epididymal inhibitory proteins, allowing the sperm's

motile potential to be realized. In addition, the glands make individual contributions to sperm preparation and support. The seminal vesicles secrete **semen**, a mucoid yellowish material containing nutrients and sperm-activating substances such as fructose, citrate, inositol, prostaglandins, and fibrinogen. Carbohydrates such as fructose provide a source of energy for the sperm mitochondria as they power the sperm's flagellar movements. The prostaglandins are believed to aid the sperm by affecting the female genital tract—making the cervical mucus more receptive to the sperm, and dampening the peristaltic contractions of the uterus and fallopian tubes to prevent them from expelling the sperm.

The prostate gland secretes a thin, milky, and alkaline fluid during ejaculation that mixes with the contents of the vas deferens. The prostatic secretion contains calcium, zinc, and phosphate ions, citrate, acid phosphatase, and various clotting enzymes. The clotting enzymes react with the fibrinogen of the seminal fluid, forming a weak coagulum that glues the semen inside the vagina and facilitates the passage of sperm through the cervix in larger numbers. The alkalinity imparted to semen by the prostate counteracts vaginal acidity, which is a natural defense against microbial pathogens and which can kill sperm or impair sperm motility. By titrating the acidity, the prostate ensures that the sperm can elude this antimicrobial defense.

Capacitation in the Female Reproductive Tract Ejaculated sperm is not immediately capable of fertilizing the female oocyte. In the first few hours after ejaculation, the spermatozoa must undergo **capacitation** inside the female reproductive tract. This is the final step in preparation for fertilization. First, the fluids of the female reproductive tract wash away more of the inhibitory factors of the male genital fluid. The flagella of the sperm hence act more readily, producing the whiplash motion that is needed for the sperm to swim to the oocyte in the fallopian tube. Second, the cell membrane of the head of the sperm is modified in preparation for the ultimate acrosomal reaction and penetration of the oocyte. Capacitation is an incompletely understood phenomenon.

Fertilization Once capacitated, the spermatozoa travel to the oocyte. There is an enormous rate of attrition among the hundreds of millions of ejaculated sperm, and at most a few hundred reach the oocyte. However, the female reproductive tract is simultaneously increasing receptivity to the male gametes (see Chapter 36).

When the few hundred sperm reach the egg, they begin to try to penetrate the granulosa cells surrounding the secondary oocyte. The sperm's acrosome contains hyaluronidase and proteolytic enzymes, which open this path. As the anterior membrane of the acrosome reaches the zona pellucida (the glycoprotein coat surrounding the oocyte), it rapidly dissolves and releases the acrosomal enzymes. Within minutes, these enzymes open a pathway through the zona pellucida for the sperm cytoplasm to merge with the oocyte cytoplasm. From beginning to end, the process of fertilization takes about half an hour.

Penile Erection and Ejaculation

The practice of internal fertilization, in which the male deposits gametes directly into the reproductive tract of the female, is at least 300 million years old. Early cartilaginous fishes probably were its innovators. These elasmobranchs retained their concepti internally until the eggs could be waterproofed and thus protected from the osmotic stress of seawater. Eventually, almost all the higher vertebrates would practice internal fertilization for the sake of defending the next generation.

For this reason, the male vertebrate possesses a special apparatus for penetrating the body of the female and delivering semen to an internal location. There are two physiologic events crucial to this internal delivery of semen: penile **erection**, which makes it possible for the penis to penetrate the vagina, bringing the urethral opening, or meatus, into close contact with the female cervix; and **ejaculation**, in which the semen is secreted into the male reproductive ductal system, mixed with sperm, and then mechanically squirted out of the penis. Both of these events are initiated and controlled by the nervous system in connection with the subjective state of sexual arousal.

Sexual Response in the Male William H. Masters and Virginia E. Johnson in 1966 described four phases of sexual response in males and females: *excitement, plateau, orgasm,* and *resolution* (FIGURE 37.7). Desire or libido precedes excitement, and testosterone is known to increase libido. Excitement that leads to erection derives from a combination of psychological factors and genital stimulation. Erotic feelings can initiate an erection without physical stimulation, and physical stimulation can initiate erection in the absence of psychological stimuli. The *pudendal nerve* transmits sensory information from the penis to the spinal cord and brain.

Erection As excitement builds in the central nervous system, efferent parasympathetic fibers in the *pelvic nerve* discharge more and more impulses

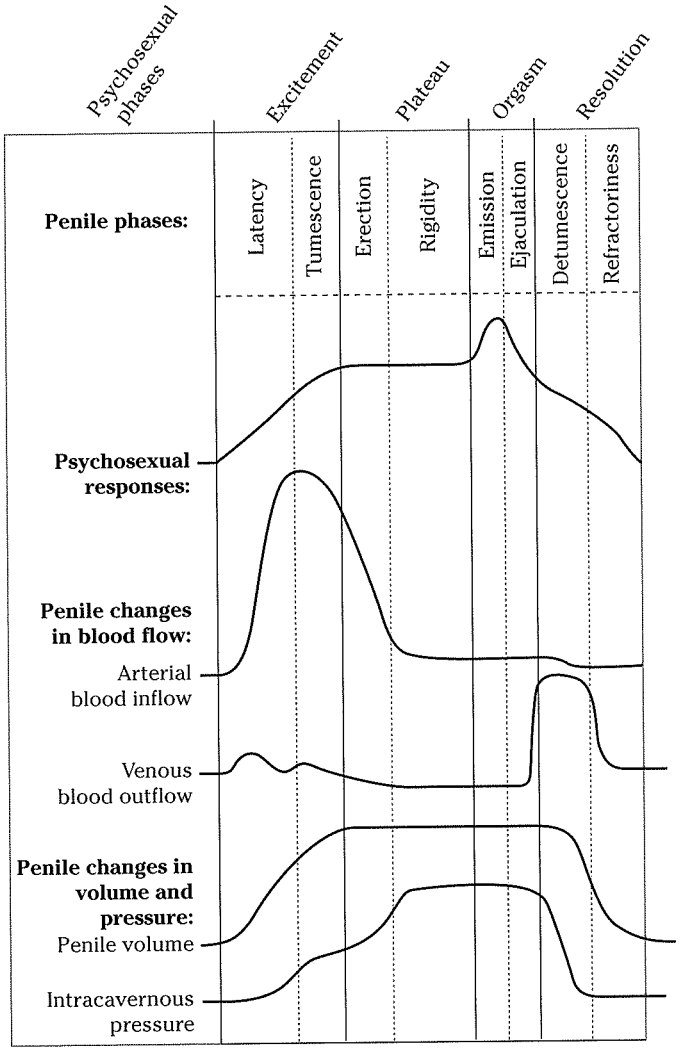


Figure 37.7 Sexual response and changes in the penis.

through the pelvic plexus to the smooth muscle of the penile cavernous artery, which runs down the center of each of the corpora cavernosa. These parasympathetic impulses lead to the secretion of nitric oxide (directly from the parasympathetic nerve terminals and also from the endothelial cells in the arterial vasculature). The nitric oxide (NO) diffuses into the smooth muscle in the wall of the cavernous artery and relaxes it. (New data suggest that testosterone is also involved in the regulation of NO secretion.) NO-mediated arterial dilation leads to up to a 60-fold increase in penile blood flow. The penis swells with blood. When the spongy tissues are stretched to their full extent, intracavernous pressure then begins to rise. The penis becomes rigid and elevates. The increasing pressure eventually compresses the cavernous veins and reduces venous outflow, building the pressure even higher.

Ejaculation As sexual excitement continues to build, bulbourethral and urethral secretions lubricate the urethra. These secretions are small in volume compared with the ejaculate, but they do contain sperm and can by themselves lead to fertilization. As genital stimulation excites the pudendal nerve more and more, a subjective sensation of **orgasm** ensues, followed immediately by the **ejaculatory spinal cord reflex**. (While the ejaculatory reflex is involuntary, it can be suppressed and delayed by input from the cerebral cortex; it is possible that at orgasm, the central nervous system releases the spinal reflex from its inhibition.) Once the reflex is initiated, sympathetic nerves stimulate the closure of the bladder neck and contraction of the ampulla of the vas deferens, the seminal vesicles, and the prostate. The contractions cause the seminal vesicles and prostate to secrete their semen into the ejaculatory duct just as the sperm are propelled from the ampulla into the ejaculatory duct. The semen briefly pools in the **posterior urethra**. This first stage of ejaculation is called **emission**.

Emission is directly followed by the rhythmic contraction of muscles surrounding the urethra: the bulbospongiosus muscle that surrounds the corpus spongiosum, the urethral smooth muscle, and other pelvic floor muscles. These contractions expel the semen from the posterior urethra and out the penile meatus in spurts.

Resolution The total ejaculate contains about 400 million sperm in about 3 to 4 mL of secretions. The normal sperm concentration ranges anywhere from 35 million to 200 million sperm per milliliter of fluid. If the sperm have been delivered into an ovulatory female reproductive tract, they now begin their journey toward the egg. Meanwhile, the resolution phase occurs a few minutes after ejaculation with *detumescence* (drainage of blood from the penis) and a *refractory period* of varying lengths, in which erection and ejaculation cannot be repeated. The cavernous arteries constrict, preventing arterial inflow, and venous outflow lowers the intracavernous pressure. As the pressure falls, the veins decompress and venous outflow increases further. This shift from net inflow to net outflow rapidly returns the penis to its flaccid state. Elastic tissues in the corpora cavernosa also assist in this shrinkage.

PATHOPHYSIOLOGY

Common problems associated with the male reproductive tract include prostatitis, erectile dysfunction, infertility, and benign and malignant growth of the prostate.

Prostatitis is inflammation of the prostate, usually due to the ascent of a urinary tract infection.

CLINICAL APPLICATION

TREATING ERECTILE DYSFUNCTION

The popular drug Viagra (generic name, sildenafil citrate), introduced in 1998, is used to treat **erectile dysfunction (ED)**. An internet search on the name at the time this chapter was written produced 17.4 million hits—an indication of the number of men seeking help for ED.

Viagra works by inhibiting the action of cGMP-specific phosphodiesterase type 5 (PDE5). PDE5 is specific to the penis. When this enzyme is inhibited, the cGMP levels in smooth muscle rise, mimicking the effect of nitric oxide on the smooth muscle of the penile cavernous arteries. The smooth muscle relaxes, and penile blood flow increases. Cross-reactivity with other PDEs can cause vasodilation elsewhere in the body, however, leading to hypotension (low blood pressure).

Some 10 to 20 million men suffer from **erectile dysfunction (ED)**, also known as *impotence*. Any cause of vascular insufficiency, including atherosclerosis, diabetes mellitus, and antihypertensive medication can lead to ED, as can psychological factors. (See Clinical Application Box *Treating Erectile Dysfunction.*)

An estimated 10% to 15% of couples cannot conceive after 1 year of trying; they are considered to have infertility. In 20% of infertile couples, the cause is never discovered. In the remaining 80%, around half of the cases of infertility are due to a problem in the male reproductive system.

Prostate cancer is by far the most common cancer in men and the second most frequent cause of male cancer deaths. Benign prostatic hyperplasia affects nearly all men as they age.

Male Infertility

Some of the causes of male **infertility** have been discussed previously. Cryptorchidism results in sterility, as the spermatogonia cannot survive at the increased temperatures of the body cavity. Other abnormalities of the testes and genital tract may also impair fertility, including varicoceles, trauma, and scarring. A careful history may reveal environmental exposures (chemical, radiation [e.g., due to cancer treatment], heat [due to tight underwear, fever, etc.]); sexually transmitted infections; mumps orchitis (which can destroy the seminiferous tubular epithelium); trauma; or previous surgery around the urogenital tract. (See Clinical Application Box *What Is a Varicocele?*)

CLINICAL APPLICATION

WHAT IS A VARICOCELE?

A 20-year-old man presents to his university health service with testicular pain. On palpation, he has a mass in the region of his left spermatic cord, and his left testicle is slightly smaller than his right. After referral to the urologist, Doppler ultrasonography confirms a backflow of blood in the pampiniform plexus of the left spermatic vein. The patient is scheduled for varicocelectomy.

A **varicocele** is a dilatation in the plexus of veins leading away from the testis along the spermatic cord. This plexus, called the *pampiniform plexus*, has no physiologic function in humans. It is an ancient and vestigial remnant from the days when our ancestors were fish. These early fish employed a disorganized venous plexus in the peritubular reabsorption and secretion of solutes from the primitive renal tubule. Later, the reproductive system came to appropriate part of the embryologic duct that had given rise to the urinary system. The reproductive system took with it this venous plexus (now useless), and through evolution, the renal tubules received a glomerular blood supply for their peritubular capillaries.

Perhaps because it is vestigial, the pampiniform plexus is vulnerable to valvular defects and a backflow of venous blood. This backflow leads to venous pooling, which in turn can lead to painful venous enlargement (varicosity) and can impair cooling of the scrotum. The heat from the pooled blood can interfere with the temperature-sensitive process of spermatogenesis. It is a very common cause of male infertility.

The workup includes a *semen analysis*, which assesses ejaculate volume, sperm count, sperm morphology and motility, semen pH, and white blood cell count. Sperm counts of less than 20 million sperm per milliliter render a male infertile. Abnormal morphology of the sperm, including multiple heads or tails and abnormally shaped heads or tails, will impair fertility. Abnormal functioning of the sperm heads (acrosomes) or tails (flagella), despite seemingly normal morphology, can also impair fertility.

A postcoital test may also be performed to evaluate the interaction between the sperm in the semen and the female cervical mucus. The inability of the sperm to penetrate the cervical mucosa may suggest an abnormality of the fluid contents of the semen or an abnormality of the acrosomal head of the sperm itself.

Analysis of serum FSH and testosterone levels may also be helpful in diagnosing testicular disease. If the testes are damaged and failing to make testosterone, the testosterone level will be low and the FSH level will be high, resulting from hypothalamic disinhibition. Thyroid function tests are also indicated (most importantly a TSH level), since abnormal thyroid function interferes with spermatogenesis.

Benign Prostatic Hyperplasia and Prostate Cancer

The development and growth of the prostate gland are stimulated by testosterone. This mitogenic (proliferative) effect on the prostate continues throughout life, often resulting in the development of **benign prostatic hyperplasia (BPH)**. As many as 20% of men are affected by BPH before the age of 40, and the number increases with age: about 70% of men at age 60 and 90% of men in their seventies show evidence of some BPH. The main symptoms of BPH result from the enlarged prostate impinging on or obstructing the urethra, and include urinary frequency, urgency, nocturia (waking at night to urinate), urinary retention, and even urinary obstruction. As its name implies, BPH is otherwise benign and is not considered to be a premalignant lesion.

Prostate cancer is a slow-growing cancer. Its incidence increases with age, and it often has an insidious onset; that is, it may grow for a long time asymptomatically before coming to the attention of the patient or his doctor. Therefore, the cancer is frequently metastatic by the time of presentation. Because prostate cancer is so common and because it has an insidious onset, the medical community encourages screening by digital rectal exam (DRE) or the prostate-specific antigen (PSA) test for men above a certain age. (There is no consensus, however, on whether such screening would reduce mortality rates.) Questionable results from a rectal exam are usually followed with transrectal ultrasound and/or an ultrasound-guided transrectal biopsy. Testosterone is a growth stimulant for prostate cancer, just as it is for BPH. Certain therapies, especially those used in cases of known metastases, therefore aim at inhibiting testosterone production or preventing testosterone from stimulating the prostatic tissue, thereby slowing the growth and spread of the cancer. Men with both BPH and prostate cancer are candidates for transurethral prostate resection (TURP).

Heart Disease Male gender is a risk factor for atherosclerosis. In 1999 in the United States, 49% more men than women died of heart disease. Many of the phenotypic differences between men and women may account for this statistic. One particular explanation may be that testosterone increases the plasma level of low-density lipoproteins (LDL, or "bad" cholesterol) and decreases the level of high-density lipoproteins (HDL, or "good" cholesterol). High LDL levels and low HDL levels are both cardiac risk factors.

Summary

- There are three principal functions of the male reproductive system: the expression of male sex characteristics, spermatogenesis (the creation of sperm), and the delivery of sperm into the female for procreation.
- Male reproduction is coordinated by the hypothalamic-pituitary-testicular (HPT) axis, which is characterized by classic negative feedback. The hypothalamus secretes GnRH, which releases FSH and LH from the pituitary.
- FSH acts on the Sertoli cells in the seminiferous tubules of the testis and stimulates spermatogenesis.
- LH acts on the Leydig cells in the testicular parenchyma and stimulates secretion of the androgen steroid, testosterone. Testosterone inhibits GnRH and FSH/LH release.
- Testosterone is converted to its active form, dihydrotestosterone (DHT), at its sites of action.
- Testosterone causes development of the male genital system in utero and at puberty. It causes growth of the genitals; hair growth; the start of spermatogenesis; deepening of the voice; protein anabolism in muscle, bone, and skin; and increased libido and aggression.
- Spermatogenesis takes place in the seminiferous tubules of the testis and has three

phases: spermatocytogenesis (mitosis and differentiation of some spermatogonia into spermatocytes), meiosis (resulting in four haploid spermatids), and spermiogenesis (the production of spermatozoa from spermatids). Testosterone and FSH promote this process.

- Newly created sperm pass from each of 900 seminiferous tubules into the epididymis of each testis. Here, sperm acquire potential motility, are bathed in inhibitory proteins, and are stored. Stored, suppressed sperm fill the vas deferens, the tube connecting the epididymis to the urethra, where they await ejaculation (expulsion from the penis) in the fluid called semen.
- Ejaculation is preceded by sexual excitement and penile erection.
- Excitement develops via psychological stimuli and tactile stimulation of the genitals. The pudendal nerve transmits afferent sensory information from the genitals to the brain.
- During excitement, the pelvic nerve transmits efferent parasympathetic impulses to the smooth muscle of the cavernous arteries in the erectile tissues of the penis, cylindrical bodies called the corpora cavernosa. These impulses dilate the penile arteries through a nitric oxide-mediated mechanism. Blood flow increases into the two dorsal corpora cavernosa and into the special ventral one, which houses the urethra; it is called the corpus spongiosum.
- When the three corpora cavernosa fill with blood, they eventually increase intracavernous pressure and reduce venous outflow, further increasing penile pressure. The penis becomes fully erect (that is, rigid and elevated).
- Increasing tactile stimulation of the pudendal nerve builds excitement until orgasm is reached, accompanied by release of the ejaculatory spinal cord reflex. The efferent limb of the reflex sends out impulses along sympathetic nerves that close the bladder neck and contract the seminal vesicles, prostate, and ampulla of the vas deferens. Contractions of urethral and pelvic muscles expel semen through the ejaculatory ducts and into the posterior urethra, an event called emission.
- If sperm are deposited into the vagina, they are capacitated, or rendered more motile and ready to fertilize, by the female reproductive tract. The acrosome, the head of the sperm cell, releases enzymes that digest a path into the oocyte, and fertilization occurs.
- Common problems associated with the male reproductive tract include prostatitis, erectile dysfunction, infertility, and benign and malignant growth of the prostate gland. Male gender is itself a cardiac risk factor.

Suggested Reading

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REVIEW QUESTIONS

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. The hypogastric nerve supplies sympathetic tone to the bladder and genitals. Its most important role in male reproductive function is probably that of stimulating:
   (A) Spermatogenesis.
   (B) Testosterone production.
   (C) Urethral lubrication.
   (D) Erection.
   (E) Detumescence.
   (F) Capacitation of sperm.
   (G) Spermiogenesis.
   (H) Ejaculation.

2. A 35-year-old man who is an avid bodybuilder complains of having developed what look like female breasts. A history reveals several years of drug abuse with a form of testosterone. Physical exam reveals acne, gynecomastia, and small testes. The mechanism behind his gynecomastia is:
   (A) Negative feedback on the hypothalamus.
   (B) Suppression of gonadal function.
   (C) Positive nitrogen balance.
   (D) Increased testosterone metabolism.
   (E) Increased testosterone action.

3. A 31-year-old man undergoes semen analysis after 1 year of trying unsuccessfully to impregnate his wife. If some of his sperm have abnormal flagella, this most likely reflects an error during which phase of sperm development?
   (A) Spermatocytogenesis
   (B) Epididymal maturation
   (C) Mixing with seminal and prostatic fluid in the posterior urethra
   (D) Spermiogenesis
   (E) Meiosis

ANSWERS TO REVIEW QUESTIONS

1. **The answer is H.** Ejaculation is mediated by sympathetic impulses from the spinal cord. Remember "point and shoot": "p" for parasympathetic mediation of erection and "s" for sympathetic mediation of ejaculation. The pudendal nerve carries afferent information to the central nervous system, and the pelvic nerve carries efferent parasympathetic impulses.

2. **The answer is D.** The drug has increased the testosterone level, thereby increasing the peripheral metabolism of testosterone to estrogen, which has proliferative effects on the breast tissue of males and females. While increased testosterone action at the androgen receptor, hypothalamic inhibition, and gonadal suppression all occur in this context, they do not cause gynecomastia.

3. **The answer is D.** Spermatids acquire their tails and become spermatozoa at the spermiogenesis phase of spermatogenesis. Thus, it is here that abnormalities in tail morphology are likely to arise. Abnormalities at other stages of sperm development are more likely to lower the sperm count or reduce sperm motility or penetrative ability.