The Endocrine System

The endocrine system provides long-term regulation and adjustment of homeostatic mechanisms and a variety of body functions. For example, the endocrine system is responsible for the regulation of fluid and electrolyte balance, cell and tissue metabolism, growth and development, and reproductive functions. The endocrine system also assists the nervous system in responding to stressful stimuli.

The endocrine system is composed of nine major endocrine glands and several other organs, such as the heart and kidneys, that have other important functions. The hormones secreted by these endocrine organs are distributed by the circulatory system to target tissues throughout the body. Each hormone affects a specific set of target tissues that may differ from that of other hormones. The selectivity is based on the presence or absence of hormone-specific receptors in the cell membrane, cytoplasm, or nucleus of the target cells.

Homeostatic regulation of circulating hormone levels primarily involves negative feedback control mechanisms. The feedback loop involves an interplay between the endocrine organ and its target tissues. Release of a particular hormone by an endocrine gland may occur in response to one of three different types of stimuli:

1. Some hormones are released in response to variations in the concentrations of specific substances in the body fluids. Parathyroid hormone, for example, is released when calcium levels decline.

2. Some hormones are released only when the gland cells receive hormonal instructions from other endocrine organs. For example, the rate of production and release of T3 and T4 by the thyroid gland is controlled by thyrotropic stimulating hormone (TSH) from the anterior pituitary gland. The secretion of TSH is in turn regulated by the release of thyrotropic releasing hormone (TRH) from the hypothalamus.

3. Some hormones are released in response to neural stimulation. The release of epinephrine and norepinephrine from the adrenal medulla during sympathetic activation is an example.

Endocrine disorders can therefore develop due to abnormalities in (a) the endocrine gland, (b) the endocrine or neural regulatory mechanisms, or (c) the target tissues. Figure A-33 provides an overview of the major classes of endocrine disorders. In the discussion that follows, we will use the thyroid gland as an example because the text introduces major types of thyroid gland disorders. These primary disorders may result in overproduction (hypersecretion) or underproduction (hyposecretion) of hormones. For example, clinicians may categorize a thyroid disorder as primary hyperthyroidism or primary hypothyroidism if the problem originates within the thyroid gland.

1. Many endocrine disorders are the result of problems within the endocrine gland itself. Causes of hyposecretion include the following:

   • *Metabolic factors*: Hyposecretion may result from a deficiency in some key substrate needed to synthesize that hormone. For example, hypothyroidism can be caused by inadequate dietary iodine levels or exposure to drugs that inhibit iodine transport or utilization at the thyroid gland.

   • *Physical damage*: Any condition that interrupts the normal circulatory supply or that physically damages the endocrine cells in some other way will suppress hormone production temporarily. If the damage is severe, the condition may be permanent. Examples of problems that may cause temporary or permanent hypothyroidism include infection or inflammation of the gland (*thyroiditis*), interruption of normal circulation, and exposure to radiation as part of treatment for cancer of the thyroid or adjacent tissues. The thyroid may also be damaged in an autoimmune disorder that results in the production of antibodies that attack and destroy normal follicle cells.

   • *Congenital disorders*: The individual may be unable to produce normal amounts of a particular hormone because (a) the gland itself is too small, (b) the required enzymes are abnormal in some way, or (c) the gland cells lack the receptors normally involved in stimulating secretory activity.

2. Endocrine disorders can also result from problems with other endocrine organs involved in the negative feedback control mechanism. For example:

   • *Secondary hypothyroidism* can be caused by inadequate TSH production at the pituitary gland or by inadequate TRH secretion at the hypothalamus.

   • *Secondary hyperthyroidism* can be caused by excessive TRH or TSH production: secondary hyperthyroidism may develop in individuals with tumors of the pituitary gland.

3. Endocrine abnormalities can also be caused by the presence of abnormal hormonal receptors in target tissues. In this case the gland and the regulatory mechanisms may be normal, but the peripheral cells are unable to respond to the circulating hormone. The best example of this type of abnormality is *type 2 diabetes* (maturity-onset, NIDDM), where peripheral cells do not respond normally to insulin. (Maturity-onset diabetes is discussed further on p. 92.)
THE SYMPTOMS OF ENDOCRINE DISORDERS

Knowledge of the individual endocrine organs and their functions makes predictions possible about the symptoms of specific endocrine disorders. For example, thyroid hormones increase basal metabolic rate, body heat production, perspiration, restlessness, and heart rate. An elevated metabolic rate, increased body temperature, weight loss, nervousness, excessive perspiration, and an increased or irregular heartbeat are common symptoms of hyperthyroidism. On the other hand, a low metabolic rate, decreased body temperature, weight gain, lethargy, dry skin, and a reduced heart rate often accompany hypothyroidism. The symptoms associated with over- and under-production of major hormones are summarized in Table A-19.

The Diagnosis of Endocrine Disorders

The first step in the diagnosis of an endocrine disorder is the physical examination. Several disorders produce characteristic physical signs that reflect abnormal hormone activities. Several examples were introduced in the text:

- **Cushing’s disease** results from an oversecretion of glucocorticoids by the adrenal cortex. As the condition progresses there is a shift away from the normal pattern of fat distribution in the body. Adipose tissue accumulates in the abdominal area, the lower cervical area (causing a “humpback”), and in the face, but the extremities become relatively thin.

- **Acromegaly** results from oversecretion of growth hormone in the adult. In this condition the facial features become distorted due to excessive cartilage growth, and the lower jaw protrudes, a sign known as *prognathism*. The hands and feet also become enlarged.

- **Adrenogenital syndrome** results from the over-secretion of androgens by the adrenal glands of a female. Hair growth patterns change, and the condition of *hirsutism* develops.

- **Hypothyroidism** due to iodine deficiency produces a distinctly enlarged thyroid gland, or *goiter*.

- **Hyperthyroidism** can produce protrusion of the eyes, or *exophthalmos*. 
### Table A-19  Clinical Implications of Endocrine Malfunctions

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Under-production Syndrome</th>
<th>Principal Signs &amp; Symptoms</th>
<th>Over-production Syndrome</th>
<th>Principal Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone (GH)</td>
<td>Pituitary growth failure (pituitary dwarfism)</td>
<td>Retarded growth, abnormal fat distribution, low blood glucose hours after a meal</td>
<td>Gigantism, acromegaly</td>
<td>Excessive growth</td>
</tr>
<tr>
<td>Antidiuretic hormone (ADH)</td>
<td>Diabetes insipidus</td>
<td>Polyuria, dehydration, thirst</td>
<td>SIADH (syndrome of inappropriate ADH secretion)</td>
<td>Increased body weight and water content</td>
</tr>
<tr>
<td>Thyroxine (T4), triiodothyronine (T3)</td>
<td>Myxedema, cretinism</td>
<td>Low metabolic rate and body temperature; impaired physical and mental development</td>
<td>Hyperthyroidism, Graves’ disease</td>
<td>High metabolic rate and body temperature</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>Hypoparathyroidism</td>
<td>Muscular weakness, neurological problems, formation of dense bones, tetany due to low blood calcium concentrations</td>
<td>Hyperparathyroidism</td>
<td>Neurological, mental, muscular problems due to high blood calcium concentrations; weak and brittle bones</td>
</tr>
<tr>
<td>Insulin</td>
<td>Diabetes mellitus (type 1)</td>
<td>High blood glucose, impaired glucose utilization, dependence on lipids for energy; glycosuria, possibly causing coma and death</td>
<td>Excess insulin production or administration</td>
<td>Low blood glucose levels, possibly causing coma and death</td>
</tr>
<tr>
<td>Mineralocorticoids (MC)</td>
<td>Hypoaldosteronism</td>
<td>Polyuria, low blood volume, high blood potassium and low sodium concentrations</td>
<td>Aldosteronism</td>
<td>Increased body weight due to sodium and water retention; low blood potassium concentration</td>
</tr>
<tr>
<td>Glucocorticoids (GC)</td>
<td>Addison’s disease</td>
<td>Inability to tolerate stress, mobilize energy reserves, or maintain normal blood glucose concentrations</td>
<td>Cushing’s disease</td>
<td>Excessive breakdown of tissue proteins and lipid reserves; impaired glucose metabolism</td>
</tr>
<tr>
<td>Epinephrine (E), norepinephrine (NE)</td>
<td>None identified</td>
<td></td>
<td>Pheochromocytoma</td>
<td>High metabolic rate, body temperature, blood pressure and heart rate</td>
</tr>
<tr>
<td>Estrogens (females)</td>
<td>Hypogonadism</td>
<td>Sterility, lack of secondary sexual characteristics</td>
<td>Adrenogenital syndrome</td>
<td>Overproduction of androgens by innermost adrenal cortex leads to masculinization</td>
</tr>
<tr>
<td>Menopause</td>
<td>Cessation of ovulation</td>
<td>Precocious puberty</td>
<td></td>
<td>Premature sexual maturation and related behavioral changes</td>
</tr>
<tr>
<td>Androgens (males)</td>
<td>Hypogonadism (male)</td>
<td>Sterility, lack of secondary sexual characteristics</td>
<td>Adrenogenital syndrome (gynecomastia)</td>
<td>Abnormal production of estrogen, sometimes due to adrenal or interstitial cell tumors; leads to breast enlargement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Precocious puberty</td>
<td>Premature sexual maturation and related behavioral changes</td>
</tr>
</tbody>
</table>
These signs are very useful, but many other signs and symptoms related to endocrine disorders are less definitive. For example, the condition of polyuria, or increased urine production, may be the result of hyposcretion of ADH (diabetes insipidus) or a form of diabetes mellitus, and a symptom such as hypertension (high blood pressure) can be caused by a variety of cardiovascular or endocrine problems. In these instances diagnostic decisions are often based on blood tests, which can confirm the presence of an endocrine disorder by detecting abnormal levels of circulating hormones, followed by procedures that determine whether the primary cause of the problem lies within the endocrine gland, the regulatory mechanism(s), or the target tissues.

**Thyroid Gland Disorders** EAP p. 323

**Hypothyroidism** typically results from some problem involving the thyroid gland rather than with pituitary production of TSH. In primary hypothyroidism TSH levels are elevated because the pituitary gland attempts to stimulate thyroid activity, but levels of T3 (triiodothyronine) and T4 (tetraiodothyronine or thyroxine) are depressed. One form of hypothyroidism results from a mutation that affects the structure of the G-proteins at TSH receptors. The structural change reduces the receptors' sensitivity to TSH and depresses thyroid activity. Treatment of chronic hypothyroidism, such as the hypothyroidism that follows radiation exposure, usually involves the administration of synthetic thyroid hormones (thyroxine) to maintain normal blood concentrations.

A **goiter** is an enlargement of the thyroid gland. The enlargement usually indicates increased follicular size, despite a decrease in the rate of thyroid hormone production. A goiter usually develops when the thyroid gland is unable to synthesize and release adequate amounts of thyroid hormones. Under continuing TSH stimulation, thyroglobulin production accelerates and the thyroid follicles enlarge. One type of goiter occurs if the thyroid fails to obtain enough iodine to meet its synthetic requirements. (This condition is now rare in the U.S. due to the use of iodized table salt.) With treatment, over time the resting thyroid may return to its normal size.

**Hyperthyroidism**, also known as thyrotoxicosis, occurs when thyroid hormones are produced in excessive quantities. In **Graves' disease** excessive thyroid activity leads to goiter and the symptoms of hyperthyroidism. Protrusion of the eyes, or exophthalmos (eks-ahf-THAL-mos), may also appear, for unknown reasons. Graves' disease has a genetic autoimmune basis and affects many more women than men. Treatment may involve the use of antithyroid drugs, the surgical removal of portions of the glandular mass, or destruction of part of the gland by exposure to radioactive iodine. Hyperthyroidism may also result from inflammation or, rarely, thyroid tumors. In extreme cases the individual's metabolic processes accelerate out of control. During a thyrotoxic crisis, or “thyroid storm,” the subject experiences an extremely high fever, rapid heart rate, and the dangerous malfunctioning of a variety of physiological systems.

**Disorders of Parathyroid Function** EAP p. 325

When the parathyroid gland secretes inadequate or excessive amounts of parathyroid hormone, calcium concentrations move outside of normal homeostatic limits. **Hypoparathyroidism** may develop after neck surgery, especially a thyroidectomy, if the blood supply to the parathyroid glands is restricted. In other cases the primary cause of the condition is uncertain. PTH is extremely costly, and because supplies are very limited, PTH administration is not used to treat this condition, despite its probable effectiveness. As an alternative, a dietary combination of vitamin D3 and calcium can be used to elevate body fluid calcium concentrations. (As noted in Chapter 6 of the text, vitamin D3 stimulates the absorption of calcium ions across the lining of the digestive tract.)

In **hyperparathyroidism**, calcium concentrations become abnormally high. Calcium salts in the skeleton are mobilized, and bones are weakened. On X-rays the bones have a light, airy appearance because the dense calcium salts no longer dominate the tissue. CNS function is depressed, thinking slows, memory is impaired, and the individual often experiences emotional swings and depression. Nausea and vomiting occur, and in severe cases the patient may become comatose. Muscle function deteriorates, and skeletal muscles become weak. Other tissues are often affected as calcium salts crystallize in joints, tendons, and the dermis, and calcium deposits may produce masses, called kidney stones, that block filtration and conduction passages in the kidney.

Hyperparathyroidism most commonly results from a tumor of the parathyroid gland. Treatment involves the surgical removal of the overactive tissue. Fortunately there are four parathyroids, and the secretion of even a portion of one gland can maintain normal calcium concentrations.

**Disorders of the Adrenal Cortex** EAP p. 326

Clinical problems related to the adrenal gland vary depending on which groups of adrenal cells become involved. The conditions may result from changes in the functional capabilities of the adrenal cells (primary conditions) or disorders affecting the regulatory mechanisms (secondary conditions). In **hypoaldosteronism**, adrenal cells fail to produce enough aldosterone, usually either as an early sign of adrenal insufficiency or because the kidneys are not releasing adequate amounts of renin. Low
Aldosterone levels lead to excessive losses of water and sodium ions at the kidneys, and the water loss in turn leads to low blood volume and a fall in blood pressure. The resulting changes in electrolyte concentrations, including hyperkalemia (high extracellular K⁺ levels) affect transmembrane potentials, eventually causing dysfunctions in neural and muscular tissues.

Hypersecretion of aldosterone results in the condition of **aldosteronism**, or **hyperaldosteronism**. Under continued aldosterone stimulation, the kidneys retain sodium ions in exchange for potassium ions that are lost in the urine. Hypertension and hypokalemia occur as extracellular potassium levels decline. Aldosteronism increases the concentration gradient for potassium ions across cell membranes. This leads to an acceleration in the rate of potassium diffusion out of the cells and into the interstitial fluids. The reduction in intracellular and extracellular potassium levels eventually interferes with the function of excitable membranes, especially cardiac muscle cells and neurons, and kidney cells.

**Addison’s disease** may result from inadequate stimulation of the adrenal cells by ACTH or from their inability to synthesize the necessary hormones usually due to autoimmune problems or infection. Affected individuals become weak and lose weight, due to a combination of appetite loss, hypotension, and hypovolemia. They cannot adequately mobilize energy reserves, and their blood glucose concentrations fall sharply within hours after a meal. Stresses cannot be tolerated, and a minor infection or injury may lead to a sharp and fatal decline in blood pressure. A particularly interesting symptom is the increased melamin pigmentation in the skin. The ACTH molecule and the MSH molecule are similar in structure, and at high concentrations ACTH stimulates the MSH receptors on melanocytes. President John F. Kennedy suffered from this disorder.

**Cushing’s disease** results from overproduction of glucocorticoids. The symptoms resemble those of a protracted and exaggerated response to stress. (The stress response is discussed in the text on p. 334.) Glucose metabolism is suppressed, lipid reserves are mobilized, and peripheral proteins are broken down. Lipids and amino acids are mobilized in excess of the existing demand. The energy reserves are shuffled around, and the distribution of body fat changes. Adipose tissues in the cheeks and around the base of the neck become enlarged at the expense of other areas, producing a “moon-faced” appearance. The demand for amino acids falls most heavily on the skeletal muscles, which respond by breaking down their contractile proteins. This response reduces muscular power and endurance. The skin becomes thin and may develop stria, or stretch marks.

If the primary cause is ACTH oversecretion at the anterior pituitary gland, the most common source is a pituitary adenoma (a benign tumor of glandular origin). Microsurgery can be performed through the sphenoid bone to remove the adenomatous tissue. Some oncology centers use pituitary radiation rather than surgery. Several drug therapies act at the hypothalamus, rather than the pituitary gland, to prevent the release of corticotropin-releasing hormone (CRH). Alternatively, the adrenal glands can be surgically removed (a bilateral adrenalectomy), but further complications can arise as the adenoma enlarges.

The chronic administration of large doses of steroids is required in some cases to treat severe asthma and some cancers and to prevent organ transplant rejection. Prolonged use of such large doses can produce symptoms similar to those of Cushing’s disease, but such treatment is usually avoided.

### Disorders of the Adrenal Medullae

**EAP p. 328**

The overproduction of epinephrine by the adrenal medulla may reflect chronic sympathetic activation. A **pheochromocytoma** (fē-ô-kro-mō-si-TÖ-muh) is a tumor that produces epinephrine and norepinephrine in massive quantities. The tumor usually develops within the adrenal medullae, but it may also involve other sympathetic ganglia. The most dangerous symptoms are rapid and irregular heartbeat and high blood pressure; other symptoms include uneasiness, sweating, blurred vision, and headaches. This condition is rare, and surgical removal of the tumor is the most effective treatment.

### Light and Behavior

**EAP p. 328**

Exposure to sunlight can do more than stimulate a tan or promote the formation of vitamin D₃. There is evidence that daily light-dark cycles have widespread effects on the central nervous system, with melatonin playing a key role. Several studies have indicated that residents of temperate and higher latitudes in the Northern Hemisphere undergo seasonal changes in mood and activity patterns. These people feel most energetic from June through September, whereas the period of December through March finds them with relatively low spirits. (The situation in the Southern Hemisphere, where the winter and summer seasons are reversed, is just the opposite.) The degree of seasonal variation differs from individual to individual: some people are affected so severely that they seek medical attention. The observed symptoms have recently been termed **seasonal affective disorder**, or **SAD**. Individuals with SAD experience depression and lethargy and find it difficult to concentrate. Often they sleep for longer periods, perhaps 10 hours or more per day. They may also go on eating binges and have a craving for carbohydrates.

Melatonin secretion appears to be regulated by sunlight exposure, not simply by light exposure. Normal interior lights are apparently not strong...
enough or do not release the right mixture of light wavelengths to depress melatonin production. Because many people spend very little time outdoors in the winter, melatonin production increases during that season, and the depression, lethargy, and concentration problems appear to be linked to elevated melatonin levels in the blood. Comparable symptoms can be produced in a normal experimental subject by an injection of melatonin.

Many SAD patients may be successfully treated by exposure to sun lamps that produce full-spectrum light. Experiments are under way to define exactly how intense the light must be and determine the minimal effective time of exposure.

Diabetes Mellitus

There are two major types of diabetes mellitus: insulin-dependent (type 1) diabetes and non-insulin-dependent (type 2) diabetes.

The primary cause of insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes, is inadequate insulin production by the beta cells of the pancreatic islets. In this condition insulin production declines due to a drop in the number of beta cells. Glucose transport in most cells cannot occur in the absence of insulin. When insulin concentrations decline, cells can no longer absorb glucose from their surroundings. Under these conditions peripheral tissues remain glucose-starved despite the presence of adequate or even excessive amounts of glucose in the circulation.

After a meal rich in glucose, blood concentrations may become so elevated that the kidney cells cannot reclaim all of the glucose molecules entering the urine. The high urinary concentration of glucose limits the ability of the kidney to conserve water, so the individual urinates frequently and may become dehydrated. The chronic dehydration leads to disturbances of neural function (blurred vision, tingling sensations, disorientation, fatigue) and muscle weakness.

Despite the high blood concentrations, glucose cannot enter endocrine tissues, and the endocrine system responds as if glucose were in short supply. Alpha cells release glucagon, and glucocorticoid production accelerates. Peripheral tissues then breakdown lipids and proteins to obtain energy. The breakdown of large numbers of fatty acids generates molecules called ketone bodies. The accumulation of large numbers of these acids can cause a dangerous reduction in blood pH. This condition, called ketoacidosis, commonly triggers vomiting. In severe cases, it can precede a fatal coma.

Long-term treatment involves a combination of dietary control, monitoring blood glucose levels up to several times a day, and administration of insulin, either by periodic injection or through more continual subcutaneous delivery with an insulin pump. The treatment is complicated by the fact that tissue glucose demands cycle up and down, depending on physical activity, emotional state, stress, and other factors that are hard to assess or predict. It is therefore difficult to maintain stable and normal blood glucose levels over long periods of time.

Type 1 diabetes most often appears in individuals under 40 years of age. Because it frequently appears in childhood, it has been called juvenile-onset diabetes. Most people with this type of diabetes (roughly 80 percent) have circulating antibodies that target the surfaces of beta cells. The disease may therefore be an example of an autoimmune disorder, a condition that results when the immune system attacks normal body cells. (Autoimmune disorders are discussed in the text, p. 446.) Consequently, attempts have been made to prevent the appearance of type 1 diabetes with azathioprine (Imuran®), a drug that suppresses the immune system. This procedure is somewhat dangerous, however, because compromising immune function increases the risk of acquiring serious infections or developing cancer.

Non-insulin-dependent diabetes mellitus (NIDDM), or type 2 diabetes, typically affects obese individuals over 40 years of age. Because of the age factor, this condition was called maturity-onset diabetes. Unfortunately, with increased childhood obesity more teenagers are developing Type 2 diabetes mellitus. Insulin levels are normal or elevated, but peripheral tissues no longer respond normally, often due to a reduction in the number of insulin receptors. Treatment consists of weight loss and dietary restrictions that may elevate insulin production and tissue response. The drug metformin (Glucophage®) lowers blood glucose concentrations, primarily by reducing glucose synthesis and release at the liver. The use of metformin in combination with other drugs that affect glucose metabolism promises to improve the quality of life for many type 2 diabetes patients.

Up to 6 percent of the U.S. population has diabetes mellitus, over 90% with the type 2 form. Diagnosis is based on high fasting blood glucose, symptoms of diabetes plus a high random blood glucose, and an inability to reduce elevated blood glucose levels 2 hours after drinking a fixed amount of glucose. These criteria have largely replaced the 6 hour glucose tolerance test that involved drinking glucose and testing the blood glucose level multiple times over 4 to 6 hours. Probably because glucose levels cannot be stabilized adequately, even with treatment, patients with long-term diabetes mellitus often develop chronic medical problems. In general, these problems are related to cardiovascular abnormalities. The most common examples include the following:

1. Vascular changes at the retina, including proliferation of capillaries and hemorrhaging, often cause disturbances of vision. This condition is called diabetic retinopathy.
2. Changes occur in the clarity of the lens, producing cataracts.
3. Small hemorrhages and inflammation at the kidneys cause degenerative changes that can lead to kidney failure. This condition is called diabetic nephropathy.

4. A variety of neural problems appear, including nerve palsies, paresthesias and pain, and autonomic dysfunction. These disorders, collectively termed diabetic neuropathy, are probably related to disturbances in the blood supply to neural tissues, since neurons do not require insulin to absorb and utilize glucose.

5. Degenerative changes in cardiac circulation can lead to early heart attacks. For a given age group, heart attacks are 3-5 times more likely in diabetic individuals.

6. Other peripheral changes in the vascular system can disrupt normal circulation to the extremities. For example, a reduction in blood flow to the feet can lead to tissue death, ulceration, infection, and loss of toes or a major portion of one or both feet.

**Endocrinology and Athletic Performance**

One of the first endocrinological "mass experiments" on humans occurred early in World War II, when the German government administered testosterone to Nazi SS officers in an attempt to make them more aggressive. (There is no evidence that the experiment succeeded.) Nowadays, such practices are universally deposed in all civilized societies, and medical research involving humans is generally subject to tight ethical constraints and meticulous scientific scrutiny. Yet a clandestine, unscientific, and potentially quite dangerous program of "experimentation" with hormones is today being pursued by athletes in many countries. Despite being banned by the International Olympic Committee, the United States Olympic Committee, the NCAA, and the NFL, and condemned by the American Medical Association and the American College of Sports Medicine, a significant number of amateur and professional athletes continue to use hormones to improve their performance at the risk of damaging their health. Although synthetic forms of testosterone are used most often, young athletes may use any combination of testosterone, growth hormone, and a variety of synthetic hormones.

**Androgen Abuse**

The use of androgens, or "anabolic steroids," has become common with many athletes, both amateur and professional. The goal of steroid use is to increase muscle mass, endurance, and "competitive spirit." It has been suggested that as many as 30 percent of college and professional athletes use anabolic steroids (with or without growth hormone) to improve their performance. Among bodybuilders, the proportion using steroids in this country may be as high as 80 percent.

Black market sales of anabolic steroids probably exceed $100 million annually. The compounds are administered orally or by injection, typically in doses 10-1000 times higher than those normally prescribed in medical treatment. (Legitimate reasons for androgen use include the generalized wasting and debilitation of cancer or AIDS and treatment of hypogonadism.)

One supposed justification for this practice has been the unfounded opinion that compounds manufactured in the body are not only safe but "good for you." In reality the administration of natural or synthetic androgens in abnormal amounts carries unacceptable health risks. Androgens affect many tissues in a variety of ways. Known complications include (1) premature epiphyseal closure; (2) various liver problems (including jaundice and hepatic tumors); (3) prostate enlargement and urinary tract obstruction; (4) testicular atrophy and infertility; and, (5) severe acne. A link to heart attacks, impaired cardiac function, and strokes has also been suggested. Moreover, the normal regulation of androgen production involves a feedback mechanism comparable to that described for adrenal steroids earlier in this chapter. A releasing hormone stimulates the production of LH, and LH in turn stimulates the secretion of testosterone and other androgens by the interstitial cells of the testes. The circulating androgens then inhibit the production of both the releasing hormone and LH, as indicated in Figure 10-7a, p. 320. Thus when synthetic androgens are administered in high doses, they can (1) suppress the normal production of testosterone, and (2) depress the manufacture of the associated releasing hormone by the hypothalamus. *This suppression may be permanent.*

The use of androgenic "bulking agents" by female bodybuilders may not only add muscle mass but alter muscular proportions and secondary sexual characteristics. For example, women taking steroids can develop irregular menstrual periods and changes in body-hair distribution (including baldness). Finally, androgen abuse may cause a generalized depression of the immune system.

**EPO Abuse**

Because it is now being synthesized using recombinant DNA techniques, erythropoietin, or EPO, is readily available. Athletes engaged in endurance sports, such as cycling or marathon running, may use it to boost the number of oxygen-carrying red blood cells in circulation. Although this improves the oxygen content of the blood, it also makes the blood more dense, and the heart must work harder to push it around the circulatory system. Between 1991 and 1994, the deaths of 18 young, otherwise healthy European cyclists were attributed to heart failure related to EPO abuse.
The Body Systems: Clinical and Applied Topics

GHB and Clenbuterol

Androgens and EPO are known hormones with reasonably well understood effects. Because drug testing is now widespread in amateur and professional sports, people interested in "getting an edge" are experimenting with other drugs whose long-term and short-term effects are difficult to predict. Two examples are the recent use of GHB and clenbuterol by amateur athletes.

Gamma-hydroxybutyrate, or GHB, was tested for use as an anaesthetic 30 years ago and rejected in part because it was linked to epileptic seizures. In 1990 this drug appeared in health-food stores, where it was sold as an anabolic agent and diet aid. During a 5-month period in 1990, 16 cases of severe reaction to GHB were treated in San Francisco alone. Symptoms experienced included confusion, hallucination, seizures, and coma at doses from 0.25 teaspoons to 4 tablespoons.

Clenbuterol abuse is reportedly widespread, although exact numbers are difficult to obtain. Clenbuterol, sometimes used to treat asthma, mimics epinephrine by increasing the diameter of the respiratory passageways and accelerating blood flow through active skeletal muscles. Although it is also rumored to have anabolic properties, there is no evidence to support this. Heavy usage can cause severe headaches, tremors, insomnia, and potentially dangerous abnormal heartbeats. During the 1992 Olympics in Barcelona, Spain, two American athletes were disqualified because they tested positive for this drug.

CRITICAL-THINKING QUESTIONS

5-1. Pheochromocytomas are tumors of the adrenal medullae that cause hypersecretion of the hormones produced by this region of the adrenal gland. What symptoms would you associate with a person who suffers from this condition?
   a. hypertension
   b. sweating
   c. nervousness
   d. elevated metabolic rate
   e. all of the above

5-2. Fifty-year-old Barbara B. reports to the emergency room with heart palpitations (rapid, irregular heart beat). EKG recording shows atrial fibrillation. Barbara's medical history includes recent weight loss of 10 pounds and complaints of increased irritability and nervousness within the last month. Some of Barbara's abnormal diagnostic and lab test results are as follows:
   Radioactive iodine uptake test (RAIU) at 2 hours: 20% absorption (normal: 1-13%)
   Serum thyroxine (T₄) test: 13 ng/dl
   Serum triiodothyronine (T₃) test: 210 ng/dl
   Serum TSH: <0.1

   What is the probable diagnosis?
   a. hypothyroidism
   b. hyperthyroidism
   c. myxedema
   d. goiter

5-3. Bill develops a benign tumor of the parathyroid glands that causes the level of parathyroid hormone in his blood to be higher than normal. Which of the following would you expect to occur as a result of this condition?
   a. decreases in the blood levels of calcium
   b. convulsions
   c. decreased muscle strength
   d. increased bone density
   e. all of the above

5-4. Sixteen-year-old John is a promising athlete who is below the average height for his age. He wants to play football in college but is convinced that he needs to be taller and stronger in order to accomplish his dream. He persuades his parents to visit a doctor and inquire about GH treatments. If you were his physician, what would you tell him about the potential risks and benefits of such treatments?

5-5. Angie is diagnosed with abnormal peripheral vision. After performing several tests, her physician decides to remove a tumor of her pituitary gland. Shortly after the surgery, her eyesight returns to normal. What was the apparent cause of Angie's problem?

5-6. A patient is suffering from secondary hypothyroidism. Assuming you had available all the modern testing materials, how could you determine if the problem was due to hypothalamic or pituitary dysfunction?