THE ENDOCRINE SYSTEM AND ITS DISORDERS

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 nonendocrine functions as well. 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 those affected by other hormones. The selectivity is based on the presence or absence of hormone-specific receptors in the target cell's cell membrane, cytoplasm, or nucleus. As researchers learn more about how cells interact, they are discovering that tissues contain a variety of molecules secreted by cells to affect their neighbors and coordinate tissue activities. The terms local hormones or cytokines have been used to describe these molecules. Although they initially thought that their effects were limited to their tissues of origin, it is now clear that many have more widespread impact. How their effects are coordinated with those of the "traditional" hormones of the endocrine system has yet to be determined.

A CLASSIFICATION OF ENDOCRINE DISORDERS

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

1. **Some hormones are released in response to variations in the concentrations of specific substances in 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 triiodothyronine ($T_3$) and tetraiodothyronine ($T_4$, thyroxine) by the thyroid gland is controlled by thyroid-stimulating hormone (TSH) from the anterior pituitary gland. The secretion of TSH is in turn regulated by the release of thyrotropin-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 the endocrine gland, the endocrine or neural regulatory mechanisms, or the target tissues. Figure 106 provides an overview of the major classes of endocrine disorders. In the discussions that follow, we will first consider primary disorders that originate in an
endocrine gland itself and that may result in hormone overproduction (hypersecretion) or underproduction (hyposcretion). We will use the thyroid gland as an example.

**DISORDERS DUE TO ENDOCRINE GLAND ABNORMALITIES**

Most endocrine disorders are the result of problems within the endocrine gland itself. Causes of hyposcretion include the following:

- **Metabolic factors.** Hyposcretion may result from a deficiency in some key substrate needed to synthesize the hormone in question. For example, hypothyroidism can be caused by inadequate dietary iodine levels or by 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 may cause them to become inactive immediately or after an initial surge of hormone release. If the damage is severe, the gland can become permanently inactive. For instance, temporary or permanent hypothyroidism can result from infection or inflammation of the gland (thyroiditis), from the interruption of normal blood flow, or from exposure to radiation as part of treatment for cancer of the thyroid gland or adjacent tissues. The thyroid gland can also be damaged in an autoimmune disorder that results in the production of antibodies that attack and destroy normal follicle cells.

- **Congenital disorders.** An individual may be unable to produce normal amounts of a particular hormone because (1) the gland itself is too small, (2) the required enzymes are abnormal, (3) the receptors that trigger secretion are relatively insensitive due to a mutation that affects G protein structure, or (4) the gland cells lack the receptors normally involved in stimulating secretory activity.

**DISORDERS DUE TO ENDOCRINE OR NEURAL REGULATORY MECHANISM ABNORMALITIES**

Endocrine disorders can result from problems with other endocrine organs involved in the negative feedback control mechanisms. 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 also develop in individuals with tumors of the pituitary gland.

■ DISORDERS DUE TO TARGET TISSUE ABNORMALITIES

Endocrine abnormalities can also be caused by the presence of abnormal hormonal receptors in target tissues. In such a case, the gland involved and the regulatory mechanisms are 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, in which peripheral cells do not respond normally to insulin.

■ SYMPTOMS AND DIAGNOSIS OF ENDOCRINE DISORDERS

Knowledge of the individual endocrine organs and their functions makes it possible to predict the symptoms of specific endocrine disorders. For example, thyroid hormones increase basal metabolic rate, body heat production, perspiration, and heart rate. An elevated metabolic rate, increased body temperature, weight loss, nervousness, excessive perspiration, and an increased or irregular heartbeat are symptoms of hyperthyroidism. Conversely, a low metabolic rate, decreased body temperature, weight gain, lethargy, dry skin, and a reduced heart rate typically accompany hypothyroidism.

The next step in the diagnosis of an endocrine disorder, after obtaining a patient’s medical history, is the physical examination. Several disorders produce characteristic physical signs that reflect abnormal hormone activities. Examples include:

• Cushing’s disease, which results from an oversecretion of glucocorticoids by the adrenal cortex. As the condition progresses, the normal pattern of fat distribution in the body shifts. Adipose tissue accumulates in the abdominal area, the lower cervical area (causing a “buffalo hump”), and the face (producing a “moon-face”), but the limbs become relatively thin.

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

• Adrenogenital syndrome, which results from the oversecretion of androgens by the adrenal glands in females. Hair growth patterns change to resemble that of males, and hirsutism (pp. 47-48) develops.

• Hypothyroidism, which can produce a distinctly enlarged thyroid gland, or goiter.

• Hyperthyroidism, which can produce protrusion of the eyes, or exophthalmos.

These signs are very useful, but many other signs and symptoms related to endocrine disorders are less definitive. For example, polyuria, or increased urine production, can result from hyposcretion of ADH (diabetes insipidus) or the hyperglycemia caused by diabetes mellitus; a symptom such as hypertension (high blood pressure) can be caused by a variety of cardiovascular or endocrine problems. In these instances, many diagnostic decisions are based on blood and other tests, which can confirm the presence of an endocrine disorder by detecting abnormal levels of circulating hormones or metabolic products resulting from hormone action, followed by tests that determine whether the primary cause of the problem lies with the endocrine gland, the regulatory mechanisms, or the target tissues. Often, it is a pattern of several different test results that leads to the diagnosis. Table 26 provides an overview of important tests used in the diagnosis of endocrine disorders.

■ GROWTH HORMONE ABNORMALITIES

Growth hormone stimulates muscular and skeletal development. Until the epiphyseal cartilages close, it causes an increase in height, weight, and muscle mass. In extreme cases, gigantism can result. In acromegaly (akron, great), an excessive amount of GH is released after puberty, when most of the epiphyseal cartilages have already closed. Cartilages and small bones respond to the hormone, however, resulting in abnormal growth of the hands, feet, lower jaw, skull, and clavicle. Figure 51 shows a typical acromegalic individual.

Children who are unable to produce adequate concentrations of GH have pituitary growth failure. The steady growth and maturation that typically precede and accompany puberty do not occur in these individuals, who have short stature, slow epiphyseal growth, and larger-than-normal adipose tissue reserves.

• FIGURE 51

Acromegaly. Acromegaly results from the overproduction of growth hormone after the epiphyseal cartilages have closed. Bone shapes change, and cartilaginous areas of the skeleton enlarge. Notice the broad facial features and the enlarged lower jaw.
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<td>Standard x-rays of epiphyseal cartilages for estimation of &quot;bone age,&quot; based on the time of closure of epiphyseal cartilages</td>
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<td>CT scan of pituitary gland</td>
<td>Standard cross-sectional CT; contrast media may be used.</td>
<td>Determine (with increasing accuracy and cost) the size of the pituitary gland; detect pituitary tumors</td>
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<tr>
<td>MRI of pituitary gland</td>
<td>Standard MRI</td>
<td></td>
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<td>Thyroid Gland</td>
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<td>Thyroid scanning</td>
<td>A dose of radionucleotide accumulates in the thyroid, giving off detectable radiation captured to create an image of the thyroid.</td>
<td>Determines size, shape, and abnormalities of the thyroid gland; detects presence of nodules and/or tumors; hyperactive or hypoactive areas; may determine cause of a mass in the neck</td>
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<td>Ultrasound examination</td>
<td>Sound waves reflected off internal structures are used to generate a computer image.</td>
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<td>of thyroid</td>
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<td>Radioactive iodine uptake</td>
<td>Radioactive iodine is ingested and trapped by the thyroid; detector determines the amount of radiiodine taken up over a period of time.</td>
<td>Determines hyperactivity or hypoactivity of the thyroid gland. Frequently done at same time as thyroid scan.</td>
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<td>(RAIU) test</td>
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<td>Parathyroid Glands</td>
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<tr>
<td>Ultrasound examination</td>
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<td>Determines structural abnormalities of the parathyroid gland, such as enlargement</td>
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<tr>
<td>of parathyroid glands</td>
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<td>Adrenal Glands</td>
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<tr>
<td>Ultrasound of adrenal</td>
<td>Standard ultrasound</td>
<td>Determines abnormalities in adrenal gland size or shape; may detect tumors</td>
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<tr>
<td>CT scan of adrenal gland</td>
<td>Standard cross-sectional CT</td>
<td>Determines abnormalities in adrenal gland size or shape; may detect tumor (pheochromocytoma)</td>
</tr>
<tr>
<td>Adrenal angiography</td>
<td>Injection of radiopaque dye for examination of the vascular supply to the adrenal gland</td>
<td>Detects tumors and hyperplasia</td>
</tr>
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<tr>
<td>Pituitary Gland</td>
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<tr>
<td>Growth hormone (GH)</td>
<td>&gt;10 ng/ml</td>
<td>&lt;10 ng/ml on stimulation for GH suggests deficiency (found in hypopituitarism and pituitary growth failure).</td>
</tr>
<tr>
<td>Plasma ACTH</td>
<td>Adults, morning: 20–80 pg/ml Adult, late afternoon: 10–40 pg/ml</td>
<td>Elevated levels of ACTH could indicate pituitary tumor, hyperpituitarism or Addison's disease with a compensatory elevation of ACTH; decreased levels suggest hypopituitarism Cushing's disease, or carcinoma of the adrenal gland.</td>
</tr>
<tr>
<td>Serum TSH</td>
<td>Adults: &lt;0.4–5.0 μU/ml</td>
<td>Elevated levels indicate hyperpituitarism or primary hypothyroidism; decreased levels suggest hypopituitarism or hyperthyroidism.</td>
</tr>
<tr>
<td>Serum LH</td>
<td>Premenopausal females: 3–30 mIU/ml Females, mid-menstrual cycle: 30–100 mIU/ml</td>
<td>Elevated levels occur with pituitary tumors and hyperpituitarism; decreased levels occur in hypopituitarism and adrenal tumors.</td>
</tr>
<tr>
<td>Diagnostic Procedure</td>
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<td>Adults: 1.0–2.3 ng/dl</td>
<td>Elevated levels occur in hyperthyroidism; decreased levels occur in hypothyroidism.</td>
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<td>Calcitonin (plasma)</td>
<td>Adult males: &lt;40 pg/ml Adult females: &lt;20 pg/ml</td>
<td>Elevated levels occur in carcinoma of the thyroid gland.</td>
</tr>
<tr>
<td>Antithyroglobulin antibodies</td>
<td>Negative to 1:20</td>
<td>High titers occur in autoimmune disorders such as Graves’ disease.</td>
</tr>
<tr>
<td>TSH</td>
<td>0.4–6 µU/ml</td>
<td>If the TSH is high and T₄ is low, primary hypothyroidism exists; if TSH and T₄ are low, secondary hypothyroidism exists. If TSH is low and T₄ is high, primary hyperthyroidism exists; if TSH and T₄ are high, secondary hyperthyroidism exists.</td>
</tr>
<tr>
<td><strong>Parathyroid Glands</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum parathyroid hormone (PTH)</td>
<td>Adults: PTH-N, 400–900 pg/ml PTH-C, 200–600 pg/ml</td>
<td>Increased levels occur in hyperparathyroidism and hypercalcemia; decreased levels occur in hypoparathyroidism.</td>
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<tr>
<td>Serum phosphorus</td>
<td>Adults: 3.4–5.5 mg/dl</td>
<td>Increased levels occur in hypoparathyroidism; decreased levels occur in hyperparathyroidism.</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>Adults: 8.5–10.5 mg/dl</td>
<td>Decreased levels occur in hypoparathyroidism; increased levels occur in hyperparathyroidism.</td>
</tr>
<tr>
<td><strong>Adrenal Glands</strong></td>
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<tr>
<td>Plasma cortisol</td>
<td>Adults, morning: 5–23 µg/dl Adults, afternoon: 3–13 µg/dl</td>
<td>Increased levels occur in adrenal hyperactivity, Cushing’s disease, stress, and steroid use; decreased levels in Addison’s disease and pituitary insufficiency.</td>
</tr>
<tr>
<td>Serum aldosterone</td>
<td>Adults: 4–30 ng/dl supine: decreased &lt;1 ng/dl elevated &gt;9 ng/dl</td>
<td>Increased levels occur in dehydration, hyperactivity of adrenal glands; and hypokalemia; decreased levels occur in hyperkalemia and adrenal hypoactivity.</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>Adults: 135–145 mEq/l</td>
<td>Increased levels occur in dehydration; decreased levels occur with adrenocortical insufficiency.</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Adults: 3.5–5.0 mEq/l</td>
<td>Increased levels occur with hyperactivity of adrenal glands and hypoaldosteronism; decreased levels occur with hyperactivity of adrenal glands and aldosteronism.</td>
</tr>
<tr>
<td>Urine hydroxycorticoid (detects breakdown products of cortisol)</td>
<td>Adults: 2–12 mg/24 hour</td>
<td>Increased levels occur in Cushing’s disease; decreased levels occur in Addison’s disease.</td>
</tr>
<tr>
<td>Urine ketosteroids (detects metabolites of androgens)</td>
<td>Adults: 5–25 mg/24 hour</td>
<td>Increased levels occur in adrenal hyperactivity and hyperpituitarism; decreased levels occur in adrenal hypoactivity and hypopituitarism.</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
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</tr>
<tr>
<td>Glucose tolerance test (monitors serum glucose following glucose ingestion by a patient who has fasted 12 hours)</td>
<td>Adults: Results after ingestion of 75–100 g of glucose: 0 hour, 75–115 mg/dl 1/2 hour, &lt;160 mg/dl 1 hour, &lt;170 mg/dl 2 hours, &lt;140 mg/dl</td>
<td>Increased levels occur in diabetes mellitus, Cushing’s disease, alcoholism, and infections; decreased levels occur in hyperinsulinism and hypoactivity of adrenal glands. (The 0-hour and 2-hour results are usually sufficient for diagnosis.)</td>
</tr>
<tr>
<td>Serum insulin</td>
<td>Adults: 5–25 µU/ml</td>
<td>Increased levels occur in early type 2 diabetes and obesity; decreased levels occur in type 1 diabetes.</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (AIC)</td>
<td>Adults: 3.8–6.4%</td>
<td>Increased levels occur in diabetes mellitus and are associated with serious chronic health complications.</td>
</tr>
</tbody>
</table>
Normal growth patterns can be restored by the injected administration of GH. Before the advent of gene splicing and recombinant DNA techniques, GH had to be carefully extracted and purified from the pituitary glands of cadavers, at considerable expense and risk of infectious disease. Now genetically manipulated bacteria are used to produce human GH in commercial quantities. The current availability of purified human growth hormone has led to its use under medically questionable circumstances. For example, it is now being praised as an “antiaging” miracle cure. Although GH injections do slow or even reverse the losses in bone and muscle mass that accompany aging, continuous use is required to maintain benefits and little is known about adverse side effects that may accompany long-term use of the hormone in adults. GH is also being sought by some parents of short but otherwise healthy children. These parents view short stature as a handicap that merits treatment, and what height is considered “too short” varies with the local population norms. Whether we are considering GH treatment of adults or children, it is important to remember that GH and the somatomedins affect many different tissues and have widespread metabolic effects. For example, children exposed to GH may grow faster, but their body fat content declines drastically, and sexual maturation is delayed. The decline is associated with metabolic changes in many organs. The range and significance of these metabolic side effects are now the subjects of long-term studies. Since growth hormone is a protein that is digested and rendered ineffective if taken orally, diet supplements advertised as supplying growth hormone are probably (and fortunately) ineffective.

**THYROID GLAND DISORDERS**

Normal production of thyroid hormones controls the background rate of cellular metabolism. These hormones exert their primary effects on metabolically active tissues and organs, including skeletal muscles, the liver, and the kidneys. The inadequate production of thyroid hormones is called hypothyroidism.

Hypothyroidism typically results from some problem that involves the thyroid gland, rather than a problem with the pituitary production of TSH. In primary hypothyroidism, TSH levels are elevated, because the pituitary gland attempts to stimulate thyroid activity, but levels of T₃ and T₄ are depressed. In a fetus or infant, hypothyroidism produces cretinism (Figure 52a), a condition marked by inadequate skeletal and nervous system development and a metabolic rate as much as 40 percent below normal levels. Unless detected and treated soon after birth, significant mental retardation may occur. The condition affects approximately 1 birth out of every 5000. Hypothyroidism developing later in childhood retards growth, delays puberty, and may affect mental development.

The signs and symptoms of adult hypothyroidism, collectively known as myxedema (miks-e-DE-muh), include subcutaneous swelling, dry skin, hair loss, low body temperature, muscular weakness, and slowed reflexes. Adults with hypothyroidism are lethargic and unable to tolerate cold temperatures. Hypothyroidism may also be associated with enlargement of the thyroid gland, producing a distinctive swelling called a goiter (Figure 52b). The enlargement generally indicates an increased thyroid follicle size, but thyroxine release may be increased or decreased, depending on the cause of the goiter. Most goiters develop 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. Goiters from inadequate dietary iodide are very rare in the United States, in part due to the addition of iodine to table salt, but these conditions can be relatively common in poorer countries, especially landlocked ones (seafood is a good source of iodine). Administering iodine may not solve the problem entirely: The sudden availability of iodine can temporarily produce symptoms of hyperthyroidism as the stored thyroglobulin becomes available.

In the absence of iodine deficiency, the usual therapy for hypothyroidism is hormone replacement therapy. This therapy often involves the administration of synthetic thyroid hormone, thyroxine, which has a negative feedback effect on the hypothalamus and pituitary gland, thus inhibiting the production of TSH. Over time, the resting thyroid may return to its normal size. Treatment of chronic hypothyroidism, such as the hypothyroidism that follows radiation exposure or autoimmune thyroiditis, generally involves the administration of thyroxine to maintain normal blood concentrations.

Hyperthyroidism, or thyrotoxicosis, occurs when thyroid hormones are produced in excessive quantities, and may be associated with slight enlargement of the thyroid. The metabolic rate climbs, and the skin may be flushed and moist with perspiration. Blood pressure and heart rate increase, and the heartbeat may become irregular. The effects on the central nervous system make the individual restless, excitable, and subject to insomnia and shifts in mood and emotional states. Despite the drive for increased activity, the person has limited energy and fatigues easily. Graves' disease is a form of hyperthyroidism that develops when anti-
bodies are produced that attack the thyroid gland. This autoimmune condition results in the release of excessive amounts of thyroid hormones, accompanied by goiter formation and other signs of hyperthyroidism. Protrusion of the eyes, or exophthalmos (ek-soh-FHAL-mohz), may also appear for unknown reasons. Graves' disease has a genetic autoimmune basis and affects many more women than it does men. Treatment may involve the use of antithyroid drugs, the surgical removal of portions of the glandular mass, or the 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 individual experiences a high fever, a rapid heart rate, and the dangerous malfunctioning of a variety of physiological systems.

### Disorders of the Adrenal Cortex

Clinical problems related to the adrenal gland vary with the zone involved. The problems may result from changes in the functional capabilities of the adrenal cells (primary conditions) or disorders that affect the regulatory mechanisms (secondary conditions).

In hypoaldosteronism, the zona glomerulosa fails to produce enough aldosterone, generally 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 dysfunction in neural and muscular tissues.

Hypersecretion of aldosterone results in aldosteronism, or hyperaldosteronism. Under continued aldosterone stimulation, the kidneys retain sodium ions in exchange for potassium ions that are lost in urine. Hypertension and hypokalemia occur as extracellular potassium levels decline, increasing the concentration gradient for potassium ions across cell membranes. This increase leads to an acceleration in the rate of potassium diffusion out of the cells and into 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 (Figure 53a) results from inadequate stimulation of the zona fasciculata by the pituitary hormone ACTH (adrenocorticotropic hormone) or, more commonly, from the inability of the adrenal cells to synthesize the necessary hormones, generally from adrenal cell loss caused by autoimmune problems or infection. Affected individuals produce insufficient levels of glucocorticoids. They become weak and lose weight, owing to a combination of appetite loss, hypotension, and hypovolemia. They cannot adequately mobilize energy reserves, and their blood glucose concentrations may fall sharply within hours after a meal. Stresses cannot be tolerated, and a minor infection or injury can lead to a sharp and even fatal decline in blood pressure. A particularly interesting symptom of adrenal insufficiency is the increased production of the pigment melanin in the skin. The ACTH molecule and the melanocyte-stimulating hormone (MSH) molecule are similar in structure, and at high concentrations ACTH stimulates the MSH receptors on melanocytes. President John F. Kennedy had Addison's disease.

Addison's disease is treated by replacement corticosteroid drugs (cortisone, prednisone, and others). However, chronic use or higher doses of corticosteroids to treat inflammatory conditions, such as rheumatoid arthritis or asthma, carries the risk of suppressing ACTH secretion and causing a secondary form of Addison's disease if the corticosteroid treatment is stopped. For this reason corticosteroids are used for these conditions only when they are unresponsive to other treatments.

Cushing's disease (Figure 53b) results from the overproduction of glucocorticoids. The symptoms resemble those of a protracted and exaggerated response to stress. 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 striae, or stretch marks.

If the primary cause of Cushing’s disease is ACTH oversecretion at the anterior lobe of the 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 pharmacological therapies act at the hypothalamus, rather than at the pituitary gland, to prevent the release of corticotropin-releasing hormone (CRH). The drugs used are serotonin antagonists, gammabutyric acid (GABA) transaminase inhibitors, or dopamine agonists. Alternatively, a bilateral adrenalectomy (the removal of the adrenal glands) can be performed, but further complications may arise as the adenoma in the pituitary gland enlarges. Cushing’s disease also results from the production of ACTH outside the pituitary gland; for example, the condition may develop with one form of lung cancer (oat cell carcinoma). The removal of the causative tumor in some cases relieves the symptoms.

As mentioned in the discussion of Addison’s disease, the chronic administration of large doses of steroids is sometimes required to treat severe asthma, arthritis, and certain cancers or to prevent transplanted organs from being rejected. Prolonged use of such large doses can produce symptoms similar to those of Cushing’s disease, which provides another reason to avoid such treatment if at all possible.

The zona reticularis ordinarily produces a negligible amount of androgens. If a tumor forms there, androgen secretion may increase dramatically, producing symptoms of adrenogenital syndrome. In women, this condition leads to the gradual development of male secondary sex characteristics, including body and facial hair patterns, adipose tissue distribution, and muscle development. Tumors affecting the zona reticularis of males can result in the production of large quantities of estrogens. Affected males develop enlarged breasts (called gynecomastia [gynaikos, woman + mastos, breast]) and, in some cases, other female secondary sex characteristics.

## DISORDERS OF THE ADRENAL MEDULLA

The overproduction of epinephrine by the adrenal medullae may reflect chronic sympathetic activation. A phaeochromocytoma (fē-ō-krom-o-sī-tō-muh) is a tumor that produces catecholamines in massive quantities. The tumor generally develops within an adrenal medulla, but may also involve other sympathetic ganglia. The most dangerous symptoms are episodes of rapid and irregular heartbeat and high blood pressure; other symptoms include uneasiness, sweating, blurred vision, and headaches. The condition is rare, and surgical removal of the tumor is the most effective treatment.

## LIGHT AND BEHAVIOR

Exposure to sunlight can do more than induce a tan or promote the formation of vitamin D. Evidence indicates 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, and they experience relatively low spirits from December through March. (The opposite situation occurs in the Southern Hemisphere, where winter and summer are reversed relative to the Northern Hemisphere.) The degree of seasonal variation differs from individual to individual: Some people display no symptoms; other people are affected so severely that they seek medical attention. The observed symptoms are called seasonal
affective disorder (SAD). Individuals with SAD experience depression and lethargy and have difficulty concentrating. They tend to sleep for long periods, perhaps 10 hours or more a day. They may also go on eating binges and crave carbohydrates.

Melatonin secretion appears to be regulated by exposure to sunlight, not simply by exposure to light. 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 then; the depression, lethargy, and concentration problems appear to be linked to elevated melatonin levels in blood. In experiments, comparable symptoms can be produced in a healthy individual by an injection of melatonin.

Many individuals with SAD are 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 to determine the minimal effective time of exposure. Some people have been using melatonin obtained (in varying doses and purity) from health-food stores to treat insomnia and jet lag. Because the health-food market is unregulated and few, if any, controlled studies have been done, it remains unclear whether melatonin is truly an effective therapy for sleep disorders or whether it aggravates SAD and depression.

**DIABETES MELLITUS**

Diabetes mellitus is a condition caused by inadequate production of, or sensitivity to, insulin. In the absence of insulin, blood glucose levels skyrocket, yet peripheral tissues become glucose-starved because they are unable to transport glucose into the cytoplasm. The two forms of diabetes mellitus, type 1 and type 2, affect approximately 1 percent of the U.S. population, and is increasing as obesity becomes more common. Even with treatment, patients with 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 causing partial or total blindness. This condition is called diabetic retinopathy.

2. Changes occur in the clarity of the lens, producing cataracts.

3. Small hemorrhages and inflammation at the microvasculature of 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 autonomic dysfunction, including male erectile dysfunction. These disorders, collectively termed diabetic neuropathy, are probably related to disturbances in the blood supply to neural tissues.

5. Degenerative changes in cardiac circulation can lead to accelerated coronary artery disease and early heart attacks. For a given age group, heart attacks are three to five times more likely in diabetic individuals.

6. Other peripheral changes in the vascular system can disrupt normal circulation to the limbs. 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.

**INSULIN-DEPENDENT DIABETES MELLITUS**

The primary cause of insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes, is either loss of, or inadequate insulin production by, the beta cells of the pancreatic islets. In most cells, glucose transport cannot occur in the absence of insulin. When insulin concentrations decline, cells can no longer absorb glucose; tissues remain glucose starved, despite the presence of adequate or even excessive amounts of glucose in the bloodstream. After a meal rich in glucose, blood glucose concentrations may become so elevated that the kidney cells cannot reclaim all the glucose molecules that enter the urine. The high urinary concentration of glucose limits the ability of the kidneys to conserve water, so the individual urinates frequently and may become dehydrated. The chronic hyperglycemia and dehydration leads to disturbances of neural function (blurred vision, tingling sensations, disorientation, and fatigue) and muscle weakness.

Despite 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 break down lipids and proteins to obtain the energy needed to continue functioning. The breakdown of large numbers of fatty acids promotes the generation of molecules called ketone bodies. These small molecules are metabolic acids whose accumulation in large numbers can cause a dangerous reduction in blood pH. This condition, called ketoacidosis, may trigger vomiting. In severe cases, it can progress to coma and death.

If the individual survives (an impossibility without insulin therapy), long-term treatment involves a combination of dietary control, monitoring of blood glucose levels several times a day, and the administration of insulin, either by injection or by infusion, using an insulin pump connected by tubing and a small catheter and needle to the subcutaneous tissue. The treatment is complicated by the fact that tissue glucose demands vary with food eaten, physical activity, emotional state, stress, and other factors that are hard to assess or predict. Dietary control, including the regulation of the type of food, time of meals, and amount consumed, can help reduce oscillations in blood glucose levels.

Modern insulin comes in many forms, with varying durations of activities. Single or, more commonly, multiple injections throughout the day are guided by blood glucose measurements in an attempt to approach normal homeostatic glucose regulation. At present, this testing involves needle sticks and finger pricks, but visual glucose monitors are now available and insulin injection can be avoided by using an insulin pump or nasal spray. However, it remains difficult to maintain stable and normal blood glucose levels over long periods, even with an insulin pump.

Precise glucose control has been shown to reduce and delay the onset of the serious chronic complications of diabetes. These complications include accelerated coronary artery disease, kidney failure, and microvascular complications that are the leading cause of blindness and foot amputations in the United States.

Since 1990, pancreas transplants have been used to treat diabetes in the United States. The procedure is generally limited to gravely ill patients already undergoing kidney transplantation. The graft success rate over five years is roughly 50 percent, and the procedure is controversial. Pancreatic islet transplantation has recently shown promise, but it requires a large number of islets.
(two cadaver organs are needed to serve as source), and, as with all transplants, suppression of the immune system to prevent rejection is necessary.

Another approach is the use of a **biohybrid artificial pancreas**. This procedure has been used to treat type 1 diabetes in dogs. Islet cells can be cultured in the laboratory and inserted within an artificial membrane. The membrane contains pores that allow movement of fluid, but prevent interactions between the islet cells and white blood cells that would reject them as foreign. The islet cells monitor the blood glucose concentration and secrete insulin or glucagon as needed. The biohybrid artificial pancreas can be located almost anywhere that has an adequate blood supply; in human trials, it is inserted under the skin of the abdomen.

Type 1 diabetes most commonly occurs in individuals under 40 years of age. Because it typically appears in childhood, it has been called **juvenile-onset diabetes**. Roughly 80 percent of people with this type of diabetes have circulating antibodies that target the surfaces of beta cells. The disease may therefore be an **autoimmune disorder**—a condition that results when the immune system attacks normal body cells. Consequently, attempts have been made to prevent the appearance of type 1 diabetes with **azathioprine** (Imuran), a drug that suppresses the immune system. This treatment is potentially dangerous, however, because compromising immune function indefinitely increases the risk of acquiring serious infections or of developing cancer. Type 1 diabetes is complex and probably reflects a combination of genetic and environmental factors. To date, genes associated with the development of type 1 diabetes have been localized to chromosomes 6, 11, and 18.

diabetes, although with more childhood obesity, significant numbers of adolescents are developing the disease. Type 2 diabetes is far more common than type 1, accounting for over 90 percent of all cases and occurring in an estimated 6.6 percent of the U.S. population. Some 500,000 new cases are diagnosed each year in the United States alone.

In type 2 diabetes, insulin levels are normal or elevated, but peripheral tissues no longer respond normally. Because most patients are overweight, treatment consists of weight loss and dietary restrictions that may elevate insulin production and tissue response. The drug **metformin** (Glucophage) lowers plasma 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.

A diagnosis of diabetes mellitus is based on two observations: a high fasting blood glucose and the persistence of an elevated blood glucose level two hours after drinking a fixed amount of glucose. These criteria have largely replaced the six-hour glucose tolerance test, which involved having the patient drink 75 to 100 grams of glucose and then testing the blood glucose level multiple times over four to six hours. Careful control to avoid high glucose levels and to keep the long-term marker (hemoglobin A1C) at a low level has been shown to reduce the risk of chronic kidney, eye, and cardiovascular complications.

### NON-INSULIN-DEPENDENT DIABETES MELLITUS

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 is also called **maturity-onset diabetes**.
END-OF-UNIT CLINICAL PROBLEMS

1. Jane, 33, awakens one morning with blurred vision and pain in her right eye. She sees her family physician, who determines that her sclera, conjunctiva, cornea, and ocular tension are normal but that her visual acuity is markedly reduced in that eye. An ophthalmologist is consulted and, after an exam, diagnoses optic neuritis. Jane is then referred to a neurologist, who learns that she had an earlier, previously forgotten episode of weakness and clumsiness of her left arm. That problem persisted for only two days, and Jane attributed it to lifting heavy suitcases on a trip. An MRI of her brain reveals several plaque-type lesions in the white matter of the brain but no other abnormalities. A lumbar puncture is performed, and the results are as follows:

- Pressure: 150 cm/H₂O
- Color: clear, colorless
- Glucose: 50 mg/dl
- Protein: 50 mg/dl
- Cells: no RBCs, WBC count of 6/mm³
- IgG: high ratio of IgG to other proteins
- Culture: no bacteria

What is the preliminary diagnosis?

2. Sandra is 50 years old. She has gained weight over the last year but has felt too tired and weak to exercise. She takes no medicine, but has tried taking vitamins with no response. During a physical examination, her physician notes the following signs:

- rounded “moon-shaped” face
- obesity of the trunk
- slender limbs
- muscular weakness
- blood pressure: 140/95 (normal = 120/80)

On the basis of these signs, which of the following disorders would you suspect?

a. Addison’s disease
b. Cushing’s disease
c. pheochromocytoma
d. hypoaldosteronism

Diagnostic and laboratory tests are ordered, and an appointment with an endocrinologist is arranged. A few of the pertinent test results are listed below:

- Plasma cortisol levels: 40 g/dl (taken at 7:00 A.M.)
- Plasma ACTH: 100 pg/ml (taken at 7:00 A.M.)
- X-ray of skull: erosion of the sella turcica
- MRI of pituitary gland: abnormal mass detected

What is the probable cause of Sandra’s disorder?

3. Mr. Johnson noticed pain on the left side of his chest under his arm two days after he cleaned out his garage. He thought it was from the lifting he had done and expected it to fade in a day or two. The next day the pain was stronger, and he couldn’t sleep well that night. In the morning his wife noticed a red, bumpy rash in two patches in the area of pain. When he saw his doctor that afternoon, there were clear blisters in the rash area and more red patches were appearing. All of the patches were in continuous band, three inches wide, that extended from the posterior midline across the
left side of his back and onto the anterior chest, roughly following the curve of the ribs. The doctor asked about childhood illnesses and confirmed that Mr. Johnson once had chickenpox. The physician then prescribed a medication.

What does the location and pattern of the rash suggest? What anatomical structures are involved? What is the probable diagnosis?

NOTES:

Answers to these problems can be found on page 245.