8 - Endocrine and Metabolic Disorders

Chapter 91. Principles of Endocrinology

Introduction

The endocrine system coordinates functioning between different organs through hormones, which are released into the bloodstream from specific types of cells within endocrine (ductless) glands. Once in circulation, hormones affect function of the target tissue. Some hormones exert an effect on cells of the organ from which they were released (paracrine effect), some even on the same cell type (autocrine effect). Hormones can be peptides of various sizes, steroids (derived from cholesterol), or amino acid derivatives.

Hormones bind selectively to receptors located inside or on the surface of target cells. Receptors inside cells interact with hormones that regulate gene function (eg, corticosteroids, vitamin D, thyroid hormone). Receptors on the cell surface bind with hormones that regulate enzyme activity or affect ion channels (eg, growth hormone, thyrotropin-releasing hormone).

Hypothalamic-Pituitary Relationships

Peripheral endocrine organ functions are controlled to varying degrees by pituitary hormones (see also Ch. 92). Some functions (eg, secretion of insulin by the pancreas, primarily controlled by the blood glucose level) are controlled to a minimal extent, whereas many (eg, secretion of thyroid or gonadal hormones) are controlled to a great extent. Secretion of pituitary hormones is controlled by the hypothalamus.

The interaction between the hypothalamus and pituitary (hypothalamic-pituitary axis) is a feedback control system. The hypothalamus receives input from virtually all other areas of the CNS and uses it to provide input to the pituitary. In response, the pituitary releases various hormones that stimulate certain endocrine glands throughout the body. Changes in circulating levels of hormones produced by these endocrine glands are detected by the hypothalamus, which then increases or decreases its stimulation of the pituitary to maintain homeostasis.

The hypothalamus modulates the activities of the anterior and posterior lobes of the pituitary in different ways. Neurohormones synthesized in the hypothalamus reach the anterior pituitary (adenohypophysis) through a specialized portal vascular system and regulate synthesis and release of the 6 major peptide hormones of the anterior pituitary. These anterior pituitary hormones regulate peripheral endocrine glands (the thyroid, adrenals, and gonads) as well as growth and lactation. No direct neural connection exists between the hypothalamus and the anterior pituitary. In contrast, the posterior pituitary (neurohypophysis) comprises axons originating from neuronal cell bodies located in the hypothalamus. These axons serve as storage sites for 2 peptide hormones synthesized in the hypothalamus; these hormones act in the periphery to regulate water balance, milk ejection, and uterine contraction.

Virtually all hormones produced by the hypothalamus and the pituitary are released in a pulsatile fashion; periods of such release are interspersed with periods of inactivity. Some hormones (eg, adrenocorticotropic hormone [ACTH], growth hormone, prolactin) have definite circadian rhythms; others (eg, luteinizing hormone and follicle-stimulating hormone during the menstrual cycle) have month-long rhythms with superimposed circadian rhythms.

Hypothalamic Controls

Thus far, 7 physiologically important hypothalamic neurohormones have been identified (see Table 91-1). Except for the biogenic amine dopamine, all are small peptides. Several are produced in the periphery as well as in the hypothalamus and function in local paracrine systems, especially in the GI tract. Vasoactive intestinal peptide, which also stimulates the release of prolactin, is one. Neurohormones may control the release of multiple pituitary hormones. Regulation of most anterior pituitary hormones depends on stimulatory signals from the hypothalamus; the exception is prolactin, which is regulated by inhibitory stimuli. If the pituitary stalk (which connects the pituitary to the hypothalamus) is severed,

prolactin release increases, whereas release of all other anterior pituitary hormones decreases.

Many hypothalamic abnormalities (including tumors and encephalitis and other inflammatory lesions) can alter the release of hypothalamic neurohormones. Because neurohormones are synthesized in different centers within the hypothalamus, some disorders affect only one neuropeptide, whereas others affect several. The result can be undersecretion or oversecretion of neurohormones. Clinical syndromes that result from the ensuing pituitary hormone dysfunction (eg, diabetes insipidus, acromegaly, hypopituitarism) are discussed in Ch. 92.

Anterior Pituitary Function

The cells of the anterior lobe (which constitutes 80% of the pituitary by weight) synthesize and release several hormones necessary for normal growth and development and also stimulate the activity of several target glands.

Adrenocorticotropic hormone (ACTH): ACTH is also known as corticotropin. Corticotropin-releasing hormone (CRH) is the primary stimulator of ACTH release, but antidiuretic hormone plays a role during stress. ACTH induces the adrenal cortex to release cortisol and several weak androgens, such as dehydroepiandrosterone (DHEA). Circulating cortisol and other corticosteroids (including exogenous corticosteroids) inhibit the release of CRH and ACTH. The CRH-ACTH-cortisol axis is a central component of the response to stress. Without ACTH, the adrenal cortex atrophies and cortisol release virtually ceases.

[**Table 91-1.** Hypothalamic Neurohormones]

Thyroid-stimulating hormone (TSH): TSH regulates the structure and function of the thyroid gland and stimulates synthesis and release of thyroid hormones. TSH synthesis and release are stimulated by the hypothalamic hormone thyrotropin-releasing hormone (TRH) and suppressed (by negative feedback) by circulating thyroid hormones.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH): LH and FSH control the production of the sex hormones. Synthesis and release of LH and FSH are stimulated by gonadotropin-releasing hormone (GnRH) and suppressed by estrogen and testosterone. In women, LH and FSH stimulate ovarian follicular development and ovulation (see p. 2497). In men, FSH acts on Sertoli cells and is essential for spermatogenesis; LH acts on Leydig cells of the testes to stimulate testosterone biosynthesis (see p. 2339).

Growth hormone (GH): GH stimulates somatic growth and regulates metabolism. Growth hormone-releasing hormone (GHRH) is the major stimulator and somatostatin is the major inhibitor of the synthesis and release of GH. GH controls synthesis of insulin-like growth factor 1 (IGF-1, also called somatomedin-C), which largely controls growth. Although IGF-1 is produced by many tissues, the liver is the major source. A variant of IGF-1 occurs in muscle, where it plays a role in enhancing muscle strength. It is less under control of GH than is the liver variant.

The metabolic effects of GH are biphasic. GH initially exerts insulin-like effects, increasing glucose uptake in muscle and fat, stimulating amino acid uptake and protein synthesis in liver and muscle, and inhibiting lipolysis in adipose tissue. Several hours later, more profound anti-insulin-like metabolic effects occur. They include inhibition of glucose uptake and use, causing blood glucose and lipolysis to increase, which increases plasma free fatty acids. GH levels increase during fasting, maintaining blood glucose levels and mobilizing fat as an alternative metabolic fuel. Production of GH decreases with aging. Ghrelin, a hormone produced in the fundus of the stomach, promotes GH release from the pituitary, increases food intake, and improves memory.

Prolactin: Prolactin is produced in cells called lactotrophs that constitute about 30% of the cells of the anterior pituitary. The pituitary doubles in size during pregnancy, largely because of hyperplasia and hypertrophy of lactotrophs. In humans, the major function of prolactin is stimulating milk production. Also, prolactin release occurs during sexual activity and stress. Prolactin may be a sensitive indicator of pituitary dysfunction; prolactin is the hormone most frequently produced in excess by pituitary tumors, and

it may be one of the hormones to become deficient from infiltrative disease or tumor compression of the pituitary.

Other hormones: Several other hormones are produced by the anterior pituitary. These include pro-opiomelanocortin (POMC, which gives rise to ACTH), α- and β-melanocyte-stimulating hormone (MSH), β-lipotropin (β-LPH), the enkephalins, and the endorphins. POMC and MSH can cause hyperpigmentation of the skin and are only significant clinically in disorders in which ACTH levels are markedly elevated (eg, Addison's disease, Nelson syndrome). The function of β-LPH is unknown. Enkephalins and endorphins are endogenous opioids that bind to and activate opioid receptors throughout the CNS.

Posterior Pituitary Function

The posterior pituitary releases antidiuretic hormone (also called vasopressin or arginine vasopressin) and oxytocin. Both hormones are released in response to neural impulses and have half-lives of about 10 min.

Antidiuretic hormone (ADH): ADH acts primarily to promote water conservation by the kidney by increasing the permeability of the distal tubular epithelium to water. At high concentrations, ADH also causes vasoconstriction. Like aldosterone, ADH plays an important role in maintaining fluid homeostasis and vascular and cellular hydration. The main stimulus for ADH release is increased osmotic pressure of water in the body, which is sensed by osmoreceptors in the hypothalamus. The other major stimulus is volume depletion, which is sensed by baroreceptors in the left atrium, pulmonary veins, carotid sinus, and aortic arch, and then transmitted to the CNS through the vagus and glossopharyngeal nerves. Other stimulants for ADH release include pain, stress, emesis, hypoxia, exercise, hypoglycemia, cholinergic agonists, β-blockers, angiotensin, and prostaglandins. Inhibitors of ADH release include alcohol, α-blockers, and glucocorticoids.

A lack of ADH causes central diabetes insipidus (see p. 772); an inability of the kidneys to respond normally to ADH causes nephrogenic diabetes insipidus (see p. 2424). Removal of the pituitary gland usually does not result in permanent diabetes insipidus because some of the remaining hypothalamic neurons produce small amounts of ADH. Copeptin is coproduced with ADH in the posterior pituitary. Measuring it may be useful in distinguishing the cause of hyponatremia.

Oxytocin: Oxytocin has 2 major targets: the myoepithelial cells of the breast, which surround the alveoli of the mammary gland, and the smooth muscle cells of the uterus. Suckling stimulates the production of oxytocin, which causes the myoepithelial cells to contract. This contraction causes milk to move from the alveoli to large sinuses for ejection (ie, the milk letdown reflex of nursing mothers). Oxytocin stimulates contraction of uterine smooth muscle cells, and uterine sensitivity to oxytocin increases throughout pregnancy. However, plasma levels do not increase sharply during parturition, and the role of oxytocin in the initiation of labor is unclear. There is no recognized stimulus for oxytocin release in men, although men have extremely low levels.

Endocrine Disorders

Endocrine disorders can result from dysfunction originating in the peripheral endocrine gland itself (primary disorders) or from understimulation or overstimulation by the pituitary (secondary disorders). The disorders can result in hormone overproduction (hyperfunction) or underproduction (hypofunction). Rarely, endocrine disorders (usually hypofunction) occur because of abnormal tissue responses to hormones. Clinical manifestations of hypofunction disorders are often insidious and nonspecific.

Hyperfunction: Hyperfunction of endocrine glands may result from overstimulation by the pituitary but is most commonly due to hyperplasia or neoplasia of the gland itself. In some cases, cancers from other tissues can produce hormones (ectopic hormone production). Hormone excess also can result from exogenous hormone administration. In some cases, patients take hormones without telling the physician (factitious disease). Tissue hypersensitivity to hormones can occur. Antibodies can stimulate peripheral endocrine glands, as occurs in hyperthyroidism of Graves' disease. Destruction of a peripheral endocrine gland can rapidly release stored hormone (eg, thyroid hormones in thyroiditis). Enzyme defects in the synthesis of a peripheral endocrine hormone can result in overproduction of hormones proximal to the

block. Finally, overproduction of a hormone can occur as an appropriate response to a disease state.

Hypofunction: Hypofunction of an endocrine gland can result from understimulation by the pituitary. Hypofunction originating within the peripheral gland itself can result from congenital or acquired disorders (including autoimmune disorders, tumors, infections, vascular disorders, and toxins). Genetic disorders causing hypofunction can result from deletion of a gene or by production of an abnormal hormone. A decrease in hormone production by the peripheral endocrine gland with a resulting increase in production of pituitary regulating hormone can lead to peripheral endocrine gland hyperplasia. For example, if synthesis of thyroid hormone is defective, thyroid-stimulating hormone (TSH) is produced in excessive amounts, causing goiter.

Several hormones require conversion to an active form after secretion from the peripheral endocrine gland. Certain disorders can block this step (eg, renal disease can inhibit production of the active form of vitamin D). Antibodies to the circulating hormone or its receptor can block the ability of the hormone to bind to its receptor. Disease or drugs can cause increased rate of clearance of hormones. Circulating substances may also block the function of hormones. Abnormalities of the receptor or elsewhere in the peripheral endocrine tissue can also cause hypofunction.

Laboratory Testing

Because symptoms of endocrine disorders can begin insidiously and may be nonspecific, clinical recognition is often delayed for months or years. For this reason, biochemical diagnosis is usually essential; it typically requires measuring levels of the peripheral endocrine hormone, the pituitary hormone, or both in the blood.

Free or bioavailable hormone (ie, hormone not bound to a specific binding hormone) is generally believed to be the active form. Free or bioavailable hormones are measured using equilibrium dialysis, ultrafiltration, or a solvent-extraction method to separate the free and albumin-bound hormone from the binding globulin. These methods can be expensive and time-consuming. Analog and competitive free hormone assays, although often used commercially, are not always accurate and should not be used.

Free hormone levels can also be estimated indirectly by assessing levels of the binding protein and using them to adjust levels of the total serum hormone. However, indirect methods are inaccurate if the binding capacity of the hormone-binding protein has been altered (eg, by a disorder).

Because most hormones have circadian rhythms, measurements need to be made at a prescribed time of day. Hormones that vary over short periods (eg, luteinizing hormone) necessitate obtaining 3 or 4 values over 1 or 2 h or using a pooled blood sample. Hormones with week-to-week variation (eg, testosterone) necessitate obtaining separate values a week apart.

In some cases, indirect estimates are used. For example, because growth hormone (GH) has a short serum half-life and is difficult to detect in serum, serum insulin-like growth factor 1 (IGF-1), which is produced in response to GH, is often measured as an index of GH activity. Sometimes, urine (eg, free cortisol when testing for Cushing's disease) or salivary hormone levels may be used. Whether measurement of circulating hormone metabolites indicates the amount of bioavailable hormone is under investigation.

In many cases, a dynamic test is necessary. Thus, in the case of hypofunctioning organs, a stimulating test can be used. In hyperfunction, a suppressive test can be used.

Treatment

Hypofunction disorders are usually treated by replacement of the peripheral endocrine hormone regardless of whether the defect is primary or secondary (an exception is GH replacement for pituitary dwarfism). If resistance to the hormone exists, drugs that reduce resistance can be used (eg, metformin or thiazolidinediones for type 2 diabetes mellitus). Occasionally, a hormone-stimulating drug is used.

Radiation therapy, surgery, and drugs that suppress hormone production are used to treat hyperfunction

disorders. In some cases, a receptor antagonist is used.

Aging and Endocrinology

Hormones undergo many changes as a person ages. Most hormone levels decrease. Some remain normal, including TSH, ACTH (basal), thyroxine, cortisol (basal), 1,25-dihydroxycholecalciferol, insulin (sometimes increases), and estradiol (in men). Hormones that increase, including ACTH (increased response to corticotropin-releasing hormone), follicle-stimulating hormone, sex-hormone binding globulin, and activin (in men), gonadotropins (in women), epinephrine (in the oldest old), parathyroid hormone, norepinephrine, cholecystokinin, vasoactive intestinal peptide and ADH (also loss of circadian rhythm), and atrial natriuretic factor, are associated with either receptor defects or postreceptor defects, resulting in hypofunction. Many age-related changes are similar to those in patients with hormone deficiency, leading to the hypothesis of a hormonal fountain of youth (ie, speculation that some changes associated with aging can be reversed by the replacement of one or more deficient hormones). Some evidence suggests that replacing certain hormones in the elderly can improve functional outcomes (eg, muscle strength, bone mineral density), but little evidence exists regarding effects on mortality. In some cases, replacing hormones may be harmful, as in estrogen replacement in most older women.

A competing theory is that the age-related decline in hormone levels represents a protective slowing down of cellular metabolism. This concept is based on the rate of living theory of aging (ie, the faster the metabolic rate of an organism, the quicker it dies). This concept is seemingly supported by studies on the effects of dietary restriction. Restriction decreases levels of hormones that stimulate metabolism, thereby slowing metabolic rate; this prolongs life in rodents.

Dehydroepiandrosterone (DHEA) and its sulfate levels decline dramatically with age. Despite optimism for the role of DHEA supplementation in older people, most controlled trials failed to show any major benefits.

Pregnenolone is the precursor of all known steroid hormones. As with DHEA, its levels decline with age. Studies in the 1940s showed its safety and benefits in people with arthritis, but additional studies failed to show any beneficial effects on memory and muscle strength.

Levels of GH and its peripheral endocrine hormone (IGF-1) decline with age. GH replacement in older people sometimes increases muscle mass but does not increase muscle strength (although it may in malnourished people). Adverse effects (eg, carpal tunnel syndrome, arthralgias, water retention) are very common. GH may have a role in the short-term treatment of some undernourished older patients, but in critically ill undernourished patients GH increases mortality. Secretagogues that stimulate GH production in a more physiologic pattern may improve benefit and decrease risk.

Levels of melatonin, a hormone produced by the pineal gland, also decline with aging. This decline may play an important role in the loss of circadian rhythms with aging. Estrogen replacement in older women is discussed in Ch. 247. Testosterone replacement in older men is discussed in Ch. 229.

Chapter 92. Pituitary Disorders

Introduction

The pituitary gland controls the functions of peripheral endocrine glands. Pituitary structure and function and relationships between the hypothalamus and the pituitary gland are discussed in Ch. 91.

Pituitary Lesions

Patients with hypothalamic-pituitary lesions generally present with some combination of symptoms and signs of a mass lesion (eg, headaches, visual field defects—particularly bitemporal hemianopia or the hemifield slide phenomenon [images drifting apart]—altered appetite, thirst); imaging evidence of a mass lesion as an incidental finding; or hypersecretion or hyposecretion of one or more pituitary hormones.

The most common cause of hypopituitary or hyperpituitary secretion is a pituitary or hypothalamic tumor. A pituitary tumor tends to produce an enlarged sella (sella turcica). Alternatively, an enlarged sella may represent empty sella syndrome.

Empty sella syndrome: In this disorder, the sella appears empty because it is filled with CSF, which flattens the pituitary gland against the wall of the sella. The syndrome may be congenital, primary, or secondary to injury (eg, ischemia after childbirth, surgery, head trauma, or radiation therapy). The typical patient is female (> 80%), obese (about 75%), and hypertensive (30%) and may have idiopathic intracranial hypertension (10%) or spinal fluid rhinorrhea (10%). Pituitary function in patients with empty sella syndrome is frequently normal. However, hypopituitarism may occur, as may headaches and visual field defects. Occasionally, patients have small coexisting pituitary tumors that secrete growth hormone (GH), prolactin, or ACTH. Diagnosis can be confirmed by CT or MRI. No specific therapy is needed for an empty sella alone.

Anterior lobe lesions: Hypersecretion of anterior lobe hormones (hyperpituitarism) is almost always selective. The anterior pituitary hormones most commonly secreted in excess are GH (as in acromegaly, gigantism), prolactin (as in galactorrhea), and ACTH (as in the pituitary type of Cushing's syndrome). Hyposecretion of anterior lobe hormones (hypopituitarism) may be generalized, usually due to a pituitary tumor, or is idiopathic, or may involve the selective loss of one or a few pituitary hormones.

Posterior lobe lesions: The 2 posterior lobe hormones are oxytocin and ADH. In women, oxytocin causes myoepithelial cells of the breast and myometrial cells of the uterus to contract. Oxytocin is present in men but has no proven function. Deficiency of ADH results in central diabetes insipidus (see p. 772). Excess ADH secretion results in the syndrome of inappropriate ADH secretion (see Sidebar 97-1 on p. 826).

Generalized Hypopituitarism

Generalized hypopituitarism refers to endocrine deficiency syndromes due to partial or complete loss of anterior lobe pituitary function. Various clinical features occur depending on the specific hormones that are deficient. Diagnosis involves imaging tests and measurement of pituitary hormone levels basally and after various provocative stimuli. Treatment depends on cause but generally includes removal of any tumor and administration of replacement hormones.

The many causes of hypopituitarism are listed in Table 92-1.

Symptoms and Signs

Symptoms and signs relate to the underlying disorder and to the specific pituitary hormones that are deficient or absent. Onset is usually insidious and may not be recognized by the patient; occasionally, onset is sudden or dramatic.

Most commonly, growth hormone (GH) is lost first, then gonadotropins, and finally thyroid-stimulating hormone (TSH) and ACTH. ADH deficiency is rare in primary pituitary disease but is common with stalk and hypothalamic lesions. Function of all target glands decreases when all hormones are deficient (panhypopituitarism).

Lack of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in children leads to delayed puberty (see Hypopituitarism in Children Resulting in Short Stature on p. 767). Premenopausal women develop amenorrhea, reduced libido, regression of secondary sexual characteristics, and infertility. Men develop erectile dysfunction, testicular

[**Table 92-1.** Causes of Hypopituitarism]

atrophy, reduced libido, regression of secondary sexual characteristics, and decreased spermatogenesis with consequent infertility.

GH deficiency may contribute to decreased energy but is usually asymptomatic and clinically undetectable in adults (see p. 767 for effects in children). Suggestions that GH deficiency accelerates atherosclerosis are unproved. TSH deficiency leads to hypothyroidism, with such symptoms as facial puffiness, hoarse voice, bradycardia, and cold intolerance. ACTH deficiency results in hypoadrenalism with attendant fatigue, hypotension, and intolerance to stress and infection. ACTH deficiency does not result in the hyperpigmentation characteristic of primary adrenal failure.

Hypothalamic lesions, which can result in hypopituitarism, can also disturb the centers that control appetite, causing a syndrome resembling anorexia nervosa, or sometimes hyperphagia with massive obesity.

Sheehan's syndrome, which affects postpartum women, is pituitary necrosis due to hypovolemia and shock occurring in the immediate peripartum period. Lactation does not start after childbirth, and the patient may complain of fatigue and loss of pubic and axillary hair.

Pituitary apoplexy is a symptom complex caused by hemorrhagic infarction of either a normal pituitary gland or, more commonly, a pituitary tumor. Acute symptoms include severe headache, stiff neck, fever, visual field defects, and oculomotor palsies. The resulting edema may compress the hypothalamus, resulting in somnolence or coma. Varying degrees of hypopituitarism may develop suddenly, and the patient may present with vascular collapse because of deficient ACTH and cortisol. The CSF often contains blood, and MRI documents hemorrhage.

Diagnosis

• MRI or CT

• Free thyroxine (T_4), TSH, and prolactin levels

• Cortisol levels plus provocative testing of pituitary-adrenal axis

• Sometimes other provocative testing

Clinical features are often nonspecific, and the diagnosis must be established with certainty before committing the patient to a lifetime of hormone replacement therapy. Pituitary dysfunction must be distinguished from anorexia nervosa, chronic liver disease, myotonia dystrophica, polyglandular autoimmune disease (see
Table 92-2), and disorders of the other endocrine glands. The clinical picture may be

[**Table 92-2.** Differentiation of Generalized Hypopituitarism from Other Selected Disorders]

particularly confusing when the function of more than one gland decreases at the same time. Evidence of structural pituitary abnormalities and of hormonal deficiencies should be sought with imaging and laboratory tests.

Imaging tests: Patients should undergo high-resolution CT or MRI, with contrast media as required (to rule out structural abnormalities, such as pituitary adenomas). PET is a research tool used in a few specialized centers and therefore is rarely done. When no modern neuroradiologic facilities are available, a simple cone-down lateral x-ray of the sella turcica can identify pituitary macroadenomas with a diameter > 10 mm. Cerebral angiography is indicated only when other imaging tests suggest perisellar vascular anomalies or aneurysms.

Laboratory testing: Initial evaluation should include testing for TSH and ACTH deficiencies, because both conditions are potentially life threatening. Testing for deficiencies of other hormones is also discussed elsewhere (see p. 766).

Free T_4 and TSH levels should be determined. Levels of both are usually low in generalized hypopituitarism; a pattern of normal TSH level with low free T_4 may also occur. In contrast, elevated TSH levels with low free T_4 indicate a primary abnormality of the thyroid gland.

Synthetic thyrotropin-releasing hormone (TRH), 200 to 500 µg IV given over 15 to 30 sec, may help identify patients with hypothalamic as opposed to pituitary dysfunction, although this test is not often done. Serum TSH levels are generally measured at 0, 20, and 60 min after injection. If pituitary function is intact, TSH should rise by > 5 mU/L, peaking by 30 min after injection. A delayed rise in serum TSH levels may occur in patients with hypothalamic disease. However, some patients with primary pituitary disease also show a delayed rise.

Serum cortisol levels alone are not reliable indicators of ACTH-adrenal axis function. One of several provocative tests should be done. The **short ACTH stimulation test** is a safer and less labor-intensive test for cortisol deficiency than the insulin tolerance test. In the short ACTH stimulation test, synthetic ACTH 250 µg IV or IM (standard test) or 1 µg IV (low-dose test) is given, and the blood cortisol response is measured 30 and 60 min later. Cortisol should rise significantly; a peak of < 20 µg/dL is abnormal. However, the short ACTH stimulation test is abnormal in secondary cortisol deficiency only when done at least 2 to 4 wk after onset of the deficiency; before this time, the adrenal glands have not atrophied and remain responsive to exogenous ACTH.

The **insulin tolerance test** is considered the most accurate way of evaluating ACTH (as well as GH and prolactin) reserve, but because of its demands, it is probably best reserved for patients who fail the short synacthen test (if confirmation is needed) or when a test must be done within 2 to 4 wk of a possible pituitary injury. Regular insulin at a dosage of 0.1 units/kg body weight IV is given over 15 to 30 sec, and venous blood samples are obtained to determine GH, cortisol, and glucose levels at baseline (before insulin administration) and 20, 30, 45, 60, and 90 min later. If glucose drops to < 40 mg/dL (< 2.22 mmol/L) or symptoms of hypoglycemia develop, cortisol should increase by > 7 µg/dL or to > 20 µg/dL. (CAUTION: *This test is hazardous in patients with severe documented panhypopituitarism or diabetes mellitus and in the elderly and is contraindicated in patients with coronary artery disease or epilepsy. A health care practitioner should be present during the test.*) Usually, only transient perspiration, tachycardia, and nervousness occur. If the patient complains of palpitations, loses consciousness, or has a seizure, the test should be stopped promptly by giving 50 mL of 50% glucose solution IV.

Neither the short ACTH stimulation test nor the insulin tolerance test alone will differentiate between primary (Addison's disease) and secondary (hypopituitary) adrenal insufficiency. Tests to make this distinction and to evaluate the hypothalamic-pituitary-adrenal axis are described under Addison's disease (see p. 792). An alternative provocative test that is done much less often is the corticotropin-releasing hormone (CRH) test. CRH 1 µg/kg IV is given by rapid injection. Serum ACTH and cortisol levels are measured 15 min before, then at baseline, and 15, 30, 60, 90, and 120 min after the injection. Adverse effects include temporary flushing, a metallic taste in the mouth, and slight and transient hypotension.

Prolactin levels are routinely measured. These levels are often elevated up to 5 times normal values when a large pituitary tumor is present, even if it does not produce prolactin. The tumor compresses the pituitary stalk, preventing dopamine, which inhibits pituitary prolactin production and release, from reaching the pituitary. Patients with such hyperprolactinemia often have hypogonadotropism and

secondary hypogonadism.

Measurement of basal levels of LH and FSH is most helpful in evaluating hypopituitarism in postmenopausal women not taking exogenous estrogens in whom circulating gonadotropin concentrations are normally high (> 30 mIU/mL). Although gonadotropin levels tend to be low in other patients with panhypopituitarism, overlap exists with the normal range. Levels of both hormones should increase in response to synthetic gonadotropin-releasing hormone (GnRH) at a dose of 100 µg IV, with LH peaking about 30 min and FSH peaking 40 min after GnRH administration. However, normal, diminished, or absent responses to GnRH may occur in hypothalamic-pituitary dysfunction. Normal increases in LH and FSH in response to GnRH vary. Administration of exogenous GnRH is not helpful in distinguishing primary hypothalamic disorders from primary pituitary disorders.

Screening for GH deficiency in adults is not recommended unless GH treatment is contemplated (eg, for unexplained reduced energy and quality of life in patients with hypopituitarism in which other hormones have been fully replaced). GH deficiency is suspected if ≥ 2 other pituitary hormones are deficient. Because GH levels vary by time of day and other factors and are difficult to interpret, levels of insulin-like growth factor 1 (IGF-1), which reflect GH, are used; low levels suggest GH deficiency, but normal levels do not rule it out. A provocative test of GH release (see p. 767) may be necessary.

Although the usefulness of provocative testing of pituitary function using releasing hormones remains to be established, if such testing is elected, it is most efficient to evaluate multiple hormones simultaneously. Growth hormone-releasing hormone (1 µg/kg), CRH (1 µg/kg), TRH (200 µg), and GnRH (100 µg) are given together IV over 15 to 30 sec. Glucose, cortisol, GH, TSH, prolactin, LH, FSH, and ACTH are measured at frequent intervals for the ensuing 180 min. The normal responses are the same as those delineated earlier for individual testing.

Treatment

• Hormone replacement

• Treatment of cause (eg, tumor)

Treatment is replacement of the hormones of the hypofunctioning target glands, as discussed in the pertinent chapters in this section and elsewhere in THE MANUAL. Adults ≤ 50 yr deficient in GH are now sometimes treated with GH doses of 0.002 to 0.012 mg/kg sc once/day. Benefits of treatment include improved energy and quality of life, increased body muscle mass, and decreased body fat mass. Suggestions that GH replacement can prevent an acceleration of atherosclerosis induced by GH deficiency are unproved.

When hypopituitarism is due to a pituitary tumor, specific treatment must be directed at the tumor as well as replacing hormones. The appropriate management of such tumors is controversial. If the tumor is small and does not secrete prolactin, most endocrinologists favor transsphenoidal removal. Most endocrinologists consider dopamine agonists, such as bromocriptine or the longer-acting cabergoline, the initial treatment of prolactinomas, regardless of size, if there is amenorrhea in a woman or erectile dysfunction in a man (see Galactorrhea on p. 770). Patients with macroadenomas > 2 cm with extremely high circulating levels of prolactin may require surgery or irradiation in addition to dopamine agonist treatment. Supervoltage irradiation of the pituitary may be added or used alone. With larger tumors and suprasellar extension, resection of the entire tumor, either transsphenoidally or transfrontally, may not be possible, and adjunctive supervoltage irradiation may be warranted.

In pituitary apoplexy, immediate surgery is warranted if visual field disturbances or oculomotor palsies develop suddenly or if somnolence progresses to coma because of hypothalamic compression. Although management with high-dose corticosteroids and general support may suffice in a few cases, transsphenoidal decompression of the tumor should generally be undertaken promptly.

Surgery and irradiation may be followed by the loss of other pituitary hormone functions. Irradiated patients may lose endocrine function slowly over years. Therefore, posttreatment hormonal status should be evaluated frequently, preferably at 3 and 6 mo and yearly thereafter. Such evaluation should include at

least assessment of thyroid and adrenal function. Patients may also develop visual difficulties related to fibrosis of the optic chiasm. Sellar imaging and visual field assessment should be done at least every 2 yr initially for about 10 yr, particularly if residual tumor tissue is present.

Selective Pituitary Hormone Deficiencies

Selective deficiencies of pituitary hormones may represent an early stage in the development of more generalized hypopituitarism. Patients must be observed for signs of other pituitary hormone deficiencies, and sellar imaging should be done at intervals to check for signs of a pituitary tumor.

Isolated growth hormone (GH) deficiency is responsible for many cases of pituitary dwarfism (see p. 767). Although one autosomal dominant form of complete GH deficiency is associated with a deletion of the GH structural gene, such gene defects probably account for a minority of cases. Treatment of GH deficiency in adults < 50 yr is discussed on p. 765.

Isolated gonadotropin deficiency occurs in both sexes and must be distinguished from primary hypogonadism; men have low serum testosterone levels and infertility, and women have amenorrhea, low serum estrogen levels, and infertility. A eunuchoid habitus is generally present. However, patients with primary hypogonadism (see p. 2341) have elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), whereas those with gonadotropin deficiency, either secondary (pituitary) or tertiary (hypothalamic), have low-normal, low, or unmeasurable levels of LH and FSH. Although most cases of hypogonadotropic hypogonadism involve deficiencies of both LH and FSH, in rare cases the secretion of only one is impaired. Isolated gonadotropin deficiency must also be distinguished from hypogonadotropic amenorrhea secondary to exercise, diet, or mental stress (see p. 2501). Although the history may be helpful, differential diagnosis may be impossible.

In **Kallmann syndrome,** the specific lack of gonadotropin-releasing hormone (GnRH) is associated with midline facial defects, including anosmia and cleft lip or palate, and with color blindness. Embryologic studies have shown that GnRH neurons originally develop in the epithelium of the olfactory placode and migrate into the septal-preoptic region of the hypothalamus early in development. In at least some cases, gene defects, localized to the X chromosome in the X-linked form of the disorder and termed the *KALIG-1* (Kallmann syndrome interval gene 1) gene, have been found in the adhesion proteins facilitating this neuronal migration. Administration of GnRH may be indicated (see p. 2894).

Isolated ACTH deficiency is rare. Weakness, hypoglycemia, weight loss, and decreased axillary and pubic hair suggest the diagnosis. Blood and urinary steroid levels are low and rise to normal after ACTH replacement. Clinical and laboratory evidence of other hormonal deficiencies is absent. Treatment is with cortisol replacement, as for Addison's disease (see p. 794).

Isolated thyroid-stimulating hormone (TSH) deficiency is likely when clinical features of hypothyroidism exist, serum TSH levels are not elevated, and no other pituitary hormone deficiencies exist. Serum TSH levels, as measured by immunoassay, are not always lower than normal, suggesting that the TSH secreted is biologically inactive. Administration of recombinant human TSH increases thyroid hormone levels (see also Hypothyroidism on p. 785).

Isolated prolactin deficiency has been noted rarely in women who fail to lactate after delivery. Basal prolactin levels are low and do not increase in response to provocative stimuli, such as thyroid-releasing hormone. Administration of prolactin is not indicated.

Hypopituitarism in Children Resulting in Short Stature

(Pituitary Dwarfism)

Hypopituitarism in children typically results in abnormally slow growth and short stature with normal proportions. It is usually due to a pituitary tumor but may be idiopathic. Diagnosis involves measurement of growth hormone (GH) levels at baseline and in response to pharmacologic stimuli. Treatment usually involves removal of the causative tumor and GH replacement.

Hypopituitarism in children may be generalized, involving deficiency of several pituitary hormones, but it is usually first expressed clinically as short stature resulting from deficiency of GH. Isolated deficiency of GH may also occur.

Hypopituitarism in children is usually due to a pituitary tumor (most commonly a craniopharyngioma) or is idiopathic. The combination of lytic lesions of the bone or skull and diabetes insipidus suggests Langerhans' cell histiocytosis (see p. 993). Hypothalamic or pituitary hormone deficiency as well as isolated GH deficiency may occur in patients with midline defects, such as cleft palate or septo-optic dysplasia, which involves absence of the septum pellucidum, optic nerve atrophy, and hypopituitarism. GH deficiency, either alone or in patients with other abnormalities, is hereditary in about 5% of cases.

Therapeutic radiation of the CNS for various cancers causes slowing of linear growth, which can often be linked to resulting GH deficiency. Radiation of the spine, either prophylactic or therapeutic, may further impair the growth potential of the vertebrae and further jeopardize height gain.

Symptoms and Signs

In a child with hypopituitarism, height is below the 3rd percentile, and growth velocity is < 6 cm/yr before age 4 yr, < 5 cm/yr from age 4 to 8 yr, and < 4 cm/yr before puberty. Skeletal maturation, assessed by bone age determination, is > 2 yr behind chronologic age.

Although of small stature, a child with hypopituitarism retains normal proportionality between upper and lower body segments. The child fails to begin pubertal development. However, a child with isolated GH deficiency secondary to hypopituitarism may undergo delayed pubertal development.

Growth data for height and weight should be plotted on a growth chart (auxologic assessment) for all children. When growth is abnormal, bone age should be determined from an x-ray of the left hand (by convention). In GH deficiency, skeletal maturation is usually delayed to the same extent as height. Evaluating the pituitary gland and sella turcica with CT or MRI is indicated to rule out calcifications and tumors; the sella turcica is abnormally small in 10 to 20% of patients.

Diagnosis

• Insulin-like growth factor 1 (IGF-1) levels and sometimes IGF binding protein type 3 (IGFBP-3) levels

• Usually confirmation by provocative testing

In mid to late childhood, IGF-1 levels, which reflect GH activity, are measured because GH levels are highly variable and difficult to interpret. Normal IGF-1 levels help exclude GH deficiency. However, IGF-1 levels are low in conditions other than GH deficiency, such as psychosocial deprivation, undernutrition, and hypothyroidism. Because IGF-1 levels are normally low in infancy and early childhood, they do not allow reliable discrimination between normal and subnormal in these age groups. In these children, levels of IGFBP-3 (the major carrier of IGF peptides) are measured. IGFBP-3 is less affected by undernutrition than is IGF-1.

In children with low levels of IGF-1 and IGFBP-3, GH deficiency is usually confirmed by measuring GH levels. Because basal GH levels are typically low or undetectable (except after the onset of sleep), assessment of GH levels requires provocative testing. However, provocative testing is nonphysiologic, subject to laboratory error, and poorly reproducible, and interpretation of data relies on arbitrary definitions of "normal" that vary by age and sex.

The insulin tolerance test may be the most effective provocative test for stimulating GH release. Less dangerous, but also less reliable, are tests using arginine infusion (500 mg/kg IV given over 30 min), levodopa (10 mg/kg to children; 500 mg po to adults), sleep, or 20 min of vigorous exercise. Generally, any GH level > 10 ng/mL or any response of > 5 ng/mL after a stimulus is sufficient to rule out GH deficiency. Increases in GH of < 5 ng/mL or to levels < 10 ng/mL are difficult to interpret. What constitutes a normal response, however, is arbitrary, and all provocative tests of GH secretion occasionally produce

misleading results. Because no single test is 100% effective in eliciting GH release, a 2nd provocative test should be done if the first is abnormal. GH levels generally peak 30 to 90 min after administration of insulin or the onset of arginine infusion, 30 to 120 min after levodopa, 60 to 120 min after the onset of sleep, and after 20 min of vigorous exercise. Because GH responses are generally abnormal in patients with diminished thyroid or adrenal function, testing should be conducted in these patients only after adequate hormone replacement therapy.

The value of exogenous growth hormone-releasing hormone (GHRH) alone in evaluating GH secretion is not established. In normal people, a dose of 1 µg/kg GHRH IV administered over 15 to 30 sec results in maximal but variable release of GH, typically reaching a peak about 60 min after GHRH injection. The variability in pituitary responsiveness to GHRH is consistent with the hypothesis that intermittent secretion of somatostatin, which opposes GHRH, is responsible for modulating pituitary GH output. Presumably, absent or diminished increases in GH in response to GHRH identify patients with GH deficiency, but whether the pattern of response distinguishes primary hypothalamic disease from pituitary disease is unclear. In children with GH deficiency presumably secondary to GHRH deficiency, highly variable GH responses to GHRH occur. The combination of arginine and GHRH improves the sensitivity for diagnosing GH deficiency.

Provocative testing may not detect subtle defects in the regulation of GH release. For example, in children with short stature secondary to GH secretory dysfunction, results of provocative testing for GH release are usually normal. However, serial measurements of GH levels over 12 to 24 h indicate abnormally low 12- or 24-h integrated GH secretion.

If diminished GH release is confirmed, secretion of other pituitary hormones and (if abnormal) hormones of their target peripheral endocrine glands also must be evaluated.

Treatment

• Recombinant GH supplements

Recombinant GH is indicated for all children with short stature who have documented GH deficiency. Dosing is usually from 0.03 to 0.05 mg/kg sc once/day. With therapy, height velocity often increases to 10 to 12 cm/yr in the first year and, although it increases more slowly thereafter, remains above pretreatment rates. Therapy is continued until an acceptable height is reached or growth rate falls below 2.5 cm/yr.

Adverse effects of GH therapy are few but include idiopathic intracranial hypertension (pseudotumor cerebri), slipped capital femoral epiphysis, and transient mild peripheral edema. Before the advent of recombinant GH, GH extracted from pituitary glands was used. This preparation rarely led to Creutzfeldt-Jakob disease 20 to 40 yr after treatment (see p. 1729). Pituitary-extracted GH was last used in the 1980s.

It is controversial whether short children with clinical features of GH deficiency but with normal GH secretion and normal IGF-1 levels should be treated with GH. Many experts recommend a trial of GH therapy for 6 to 12 mo, continuing GH only if there is a doubling of or an increase of 3 cm/yr over the pretreatment height velocity. Others object to this approach because it is expensive, is experimental, may lead to adverse effects, labels otherwise healthy children as abnormal, and raises ethical and psychosocial concerns that feed into the bias of "heightism."

Cortisol and thyroid hormone should be replaced throughout childhood, adolescence, and adulthood in patients with short stature due to pituitary dwarfism when circulating levels of these hormones are low (see pp. 786 and 794). When puberty fails to occur normally, treatment with gonadal sex steroids is indicated (see p. 2894).

GH therapy in children with short stature due to therapeutic radiation of the pituitary gland for cancer carries a theoretic risk of causing cancer recurrence. However, studies have not shown a greater-than-expected incidence of new cancers or a greater recurrence rate. GH replacement can probably be safely instituted at least 1 yr after the successful completion of anticancer therapy.

Gigantism and Acromegaly

Gigantism and acromegaly are syndromes of excessive secretion of growth hormone (hypersomatotropism) that are nearly always due to a pituitary adenoma. Before closure of the epiphyses, the result is gigantism. Later, the result is acromegaly, which causes distinctive facial and other features. Diagnosis is clinical and by skull and hand x-rays and measurement of growth hormone levels. Treatment involves removal or destruction of the responsible adenoma.

Many growth hormone (GH)-secreting adenomas contain a mutant form of the G_S protein, which is a stimulatory regulator of adenylate cyclase. Cells with the mutant form of G_S protein secrete GH even in the absence of growth hormone-releasing hormone (GHRH). A few cases of ectopic GHRH-producing tumors, especially of the pancreas and lung, also have been described.

Symptoms and Signs

Pituitary gigantism: This rare condition occurs if GH hypersecretion begins in childhood, before closure of the epiphyses. Skeletal growth velocity and ultimate stature are increased, but little bony deformity occurs. However, soft-tissue swelling occurs, and the peripheral nerves are enlarged. Delayed puberty or hypogonadotropic hypogonadism is also frequently present, resulting in a eunuchoid habitus.

Acromegaly: In acromegaly, GH hypersecretion usually starts between the 20s and 40s. When GH hypersecretion begins after epiphyseal closure, the earliest clinical manifestations are coarsening of the facial features (see
Plate 21) and soft-tissue swelling of the hands and feet. Appearance changes, and larger rings, gloves, and shoes are needed. Photographs of the patient are important in delineating the course of the disease.

In adults with acromegaly, coarse body hair increases and the skin thickens and frequently darkens. The size and function of sebaceous and sweat glands increase, such that patients frequently complain of excessive perspiration and offensive body odor. Overgrowth of the mandible leads to protrusion of the jaw (prognathism) and malocclusion of teeth. Cartilaginous proliferation of the larynx leads to a deep, husky voice. The tongue is frequently enlarged and furrowed. In longstanding acromegaly, costal cartilage growth leads to a barrel chest. Articular cartilaginous proliferation occurs early in response to GH excess, with the articular cartilage possibly undergoing necrosis and erosion. Joint symptoms are common, and crippling degenerative arthritis may occur.

Peripheral neuropathies occur commonly because of compression of nerves by adjacent fibrous tissue and endoneural fibrous proliferation. Headaches are common because of the pituitary tumor. Bitemporal hemianopia may develop if suprasellar extension compresses the optic chiasm. The heart, liver, kidneys, spleen, thyroid, parathyroid glands, and pancreas are larger than normal. Cardiac disease occurs in perhaps one third of patients, with a doubling in the risk of death from cardiac disease. Hypertension occurs in up to one third of patients. The risk of cancer, particularly of the GI tract, increases 2-fold to 3-fold. GH increases tubular reabsorption of phosphate and leads to mild hyperphosphatemia. Impaired glucose tolerance occurs in nearly one half the patients with acromegaly and in gigantism, but clinically significant diabetes mellitus occurs in only about 10% of patients.

Galactorrhea occurs in some women with acromegaly, usually in association with hyperprolactinemia (see p. 770). However, galactorrhea may occur with GH excess alone, because GH itself stimulates lactation. Decreased gonadotropin secretion often occurs with GH-secreting tumors. About one third of men with acromegaly develop erectile dysfunction, and nearly all women develop menstrual irregularities or amenorrhea.

Diagnosis

• CT or MRI

• Insulin-like growth factor 1 (IGF-1) levels

• Usually GH levels

Diagnosis can be made from the characteristic clinical findings. CT, MRI, or skull x-rays disclose cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica. X-rays of the hands show tufting of the terminal phalanges and soft-tissue thickening. Generally, glucose tolerance is abnormal and serum phosphate levels are mildly elevated.

Serum IGF-1 should be measured in patients with suspected acromegaly; IGF-1 levels are typically substantially elevated (3-fold to 10-fold), and because IGF-1 levels do not fluctuate like GH levels do, they are the simplest way to assess GH hypersecretion. IGF-1 levels also can be used to monitor response to therapy.

Plasma GH levels measured by radioimmunoassay are typically elevated. Blood should be taken before the patient eats breakfast (basal state); in normal people, basal GH levels are < 5 ng/mL. Transient elevations of GH are normal and must be distinguished from pathologic hypersecretion. The degree of GH suppression after a glucose load remains the standard and thus should be measured in patients with elevated plasma GH; however, the results are assay-dependent, and the cutoff for normal suppression is controversial. Secretion in normal people is suppressed to < 2 ng/mL (a cutoff of < 1 ng/mL is often used) within 90 min of administration of glucose 75 g po. Most patients with acromegaly have substantially higher values. Basal plasma GH levels are also important in monitoring response to therapy.

CT or MRI of the head should be done to look for a tumor. If a tumor is not visible, excessive secretion of pituitary GH may be due to a non-CNS tumor producing excessive amounts of ectopic GHRH. Demonstration of elevated levels of plasma GHRH can confirm the diagnosis. Lungs and pancreas may be first evaluated in searching for the sites of ectopic production.

Treatment

• Surgery or radiation therapy

Ablative therapy with surgery or radiation is generally indicated. Transsphenoidal resection is preferred, but choices vary at different institutions. Stereotactic supervoltage radiation, delivering about 5000 cGy to the pituitary, is used, but GH levels may not fall to normal for several years. Treatment with accelerated protons (heavy particle radiation) permits delivery of larger doses of radiation (equivalent to 10,000 cGy) to the pituitary; such therapy poses higher risk of cranial nerve and hypothalamic damage and is available only in a few centers. Development of hypopituitarism several years after irradiation is common. Because radiation damage is cumulative, proton beam therapy should not be used after conventional γ-irradiation. A combined approach with both surgery and radiation therapy is indicated for patients with progressive extrasellar involvement by a pituitary tumor and for patients whose entire tumor cannot be resected, which is often the case.

Surgical removal of the tumor is likely to have been curative if GH levels after the glucose tolerance test and IGF-1 levels reach normal values. If one or both values are abnormal, further therapy is usually needed. If GH excess is poorly controlled, hypertension, heart failure, and a doubling in the death rate occur. If GH levels are < 5 ng/mL, however, mortality does not increase.

In general, drug therapy is indicated if surgery and radiation therapy are contraindicated, if they have not been curative, or if radiation therapy is being given time to work. In such instances, a somatostatin analog, octreotide, is given at 0.05 to 0.15 mg sc q 8 to 12 h; it suppresses GH secretion effectively in patients refractory to bromocriptine, surgery, or irradiation. Longer-acting somatostatin analogs, such as mannitol-modified release octreotide (octreotide LAR) given 10 to 30 mg IM q 4 to 6 wk and lanreotide given 30 mg IM q 10 to 14 days, are more convenient. Bromocriptine mesylate (1.25 to 5 mg po bid) may effectively lower GH levels in a small percentage of patients but is less effective than somatostatin analogs.

Pegvisomant, a GH receptor blocker, has been shown to reduce the effects of GH and lower IGF-1 levels in people with acromegaly, without apparent increase in pituitary tumor size. This drug may find a place in treating patients who are partially or totally unresponsive to somatostatin analogs.

Galactorrhea

Galactorrhea is lactation in men or in women who are not breastfeeding. It is generally due to a prolactin-secreting pituitary adenoma. Diagnosis is by measurement of prolactin levels and imaging tests. Treatment involves tumor inhibition with dopamine agonist drugs and sometimes removal or destruction of the adenoma.

Etiology

Galactorrhea is generally due to a prolactin-secreting pituitary adenoma (prolactinoma). Most tumors in women are microadenomas (< 10 mm in diameter), but a small percentage are macroadenomas (> 10 mm) when diagnosed. The frequency of microadenomas is much lower in men, perhaps because of later recognition.

Hyperprolactinemia and galactorrhea also may be caused by ingestion of certain drugs, including phenothiazines, other antipsychotics, certain antihypertensives (especially α-methyldopa), and opioids. Primary hypothyroidism can cause hyperprolactinemia and galactorrhea, because increased levels of thyroid-releasing hormone increase secretion of prolactin as well as thyroid-stimulating hormone (TSH). It is unclear why hyperprolactinemia is associated with hypogonadotropism and hypogonadism. Causes of hyperprolactinemia are listed in
Table 92-3.

Symptoms and Signs

Abnormal lactation is not defined quantitatively; it is milk release that is inappropriate, persistent, or worrisome to the patient. Spontaneous lactation is more unusual than milk released in response to manual expression. The milk is white. Women with galactorrhea commonly also have amenorrhea or oligomenorrhea. Women with galactorrhea and amenorrhea may also have symptoms and signs of estrogen deficiency, including dyspareunia, due to inhibition of pulsatile luteinizing hormone and follicle-stimulating hormone release

[**Table 92-3.** Causes of Hyperprolactinemia]

by high prolactin levels. However, estrogen production may be normal, and signs of androgen excess have been observed in some women with hyperprolactinemia. Hyperprolactinemia may occur with other menstrual cycle disturbances besides amenorrhea, including infrequent ovulation and corpus luteum dysfunction.

Men with prolactin-secreting pituitary tumors typically have headaches or visual difficulties. About two thirds of affected men have loss of libido and erectile dysfunction.

Diagnosis

• Prolactin levels

• Thyroxine (T_4) and TSH levels

• CT or MRI

Diagnosis of galactorrhea due to a prolactin-secreting pituitary adenoma is based on elevated prolactin levels. In general, prolactin levels correlate with the size of a pituitary tumor and can be used to follow patients over time. Serum gonadotropin and estradiol levels are either low or in the normal range in women with hyperprolactinemia. Primary hypothyroidism is easily ruled out by absence of elevated TSH.

High-resolution CT or MRI is the method of choice in identifying microadenomas. Visual field examination is indicated in all patients with macroadenomas and in any patient who elects drug therapy or surveillance only.

Treatment

• Depends on cause, symptoms, and other factors

The treatment of microprolactinomas is controversial. Asymptomatic patients who have prolactin levels < 100 ng/mL and normal CT or MRI results or who have only microadenomas can probably be observed; serum prolactin often normalizes within years. Patients with hyperprolactinemia should be monitored with quarterly measurement of prolactin levels and undergo sellar CT or MRI annually for at least an additional 2 yr. The frequency of sellar imaging can then be reduced if prolactin levels do not increase. Indications for treatment in women include the desire for pregnancy, amenorrhea or significant oligomenorrhea (because of the risk of osteoporosis), hirsutism, low libido, and troublesome galactorrhea. Indications in men include hypogonadism (because of the risk of osteoporosis), erectile dysfunction, low libido, and troublesome infertility.

The initial treatment is usually a dopamine agonist such as bromocriptine (1.25 to 5 mg po bid) or the longer-acting cabergoline (0.25 to 1.0 mg po once/wk or twice/wk). Cabergoline is the treatment of choice because it seems to be more easily tolerated and more potent than bromocriptine. Women trying to become pregnant should switch to bromocriptine at least 1 mo before planned conception and stop bromocriptine use at the time of a positive pregnancy test; long-term safety data are better established for bromocriptine than for cabergoline. Exogenous estrogen can be given to women with a microadenoma who are clinically hypoestrogenic or have low estradiol levels. Exogenous estrogen is unlikely to cause tumor expansion.

Patients with macroadenomas generally should be treated with dopamine agonists or surgically but only after thorough testing of pituitary function and evaluation for radiation therapy. Dopamine agonists are usually the initial treatment of choice and usually shrink the tumor. If prolactin levels fall and symptoms and signs of compression by the tumor abate, no other therapy may be necessary. Surgery or radiation therapy may be easier to do or yield better results after tumor shrinkage induced by a dopamine agonist. Although dopamine agonist treatment usually needs to be continued long-term, prolactin-secreting tumors sometimes remit, either spontaneously or perhaps aided by the drug therapy. Sometimes, therefore, dopamine agonists can be stopped without a recurrence of the tumor or a rise in prolactin levels; remission is more likely with microadenomas than macroadenomas. Remission is also more likely after pregnancy.

High doses of dopamine agonists, particularly cabergoline and pergolide, are thought to have caused valvular heart disease in some patients with Parkinson's disease. It is not clear whether the lower doses of dopamine agonists used for hyperprolactinemia similarly increase the risk of valvular heart disease, but the possibility should be discussed with patients, and echocardiographic surveillance should be considered. The risk may be less with bromocriptine or a nonergot-derived dopamine agonist (eg, quinagolide).

Radiation therapy should be used only in patients with progressive disease who do not respond to other forms of therapy. With irradiation, hypopituitarism often develops several years after therapy. Monitoring endocrine function and sellar imaging are indicated yearly for life.

Central Diabetes Insipidus

(Vasopressin-Sensitive Diabetes Insipidus)

(See also Sidebar 97-1 on p. 826 and Nephrogenic Diabetes Insipidus on p. 2424.)

Diabetes insipidus (DI) results from a deficiency of ADH due to a hypothalamic-pituitary disorder (central DI [CDI]) or from resistance of the kidney to ADH (nephrogenic DI [NDI]). Polyuria and polydipsia develop. Diagnosis is by water deprivation test showing failure to maximally concentrate urine; ADH levels and response to exogenous ADH help distinguish CDI from NDI. Treatment is with intranasal desmopressin or lypressin. Nonhormonal treatment includes use of diuretics (mainly thiazides) and ADH-releasing drugs, such as chlorpropamide.

Pathophysiology

Polyuria may result from CDI, a deficiency of ADH, NDI, or compulsive or habitual water drinking (psychogenic polydipsia). The posterior lobe of the pituitary is the major site of ADH storage and release, but ADH is synthesized within the hypothalamus. Newly synthesized hormone can still be released into the circulation as long as the hypothalamic nuclei and part of the neurohypophyseal tract are intact. Only about 10% of neurosecretory neurons must remain intact to avoid CDI. The pathology of CDI thus always involves the supraoptic and paraventricular nuclei of the hypothalamus or a major portion of the pituitary stalk.

CDI may be complete (absence of ADH) or partial (insufficient amounts of ADH). CDI may be primary, in which there is a marked decrease in the hypothalamic nuclei of the neurohypophyseal system.

Etiology

Primary CDI: Genetic abnormalities of the ADH gene on chromosome 20 are responsible for autosomal dominant forms of primary CDI, but many cases are idiopathic.

Secondary CDI: CDI may also be secondary (acquired), caused by various lesions, including hypophysectomy, cranial injuries (particularly basal skull fractures), suprasellar and intrasellar tumors (primary or metastatic), Langerhans' cell histiocytosis (Hand-Schuller-Christian disease), granulomas (sarcoidosis or TB), vascular lesions (aneurysm and thrombosis), and infections (encephalitis or meningitis).

Symptoms and Signs

Onset may be insidious or abrupt, occurring at any age. The only symptoms in primary CDI are polydipsia and polyuria. In secondary CDI, symptoms and signs of the associated lesions are also present. Enormous quantities of fluid may be ingested, and large volumes (3 to 30 L/day) of very dilute urine (sp gr usually < 1.005 and osmolality < 200 mOsm/L) are excreted. Nocturia almost always occurs. Dehydration and hypovolemia may develop rapidly if urinary losses are not continuously replaced.

Diagnosis

• Water deprivation test

• Sometimes ADH levels

CDI must be differentiated from other causes of polyuria (see Table 92-4), particularly psychogenic polydipsia and NDI. All tests for CDI (and for NDI) are based on the principle that increasing the plasma osmolality in normal people will lead to decreased excretion of urine with increased osmolality.

The water deprivation test is the simplest and most reliable method for diagnosing CDI but *should be done only while the patient is under constant supervision. Serious dehydration may result.* Additionally, if psychogenic

[**Table 92-4.** Common Causes of Polyuria]

polydipsia is suspected, the patient must be observed to prevent surreptitious drinking. The test is started in the morning by weighing the patient, obtaining venous blood to determine electrolyte concentrations and osmolality, and measuring urinary osmolality. Voided urine is collected hourly, and its sp gr or, preferably, osmolality is measured. Dehydration is continued until orthostatic hypotension and postural tachycardia appear, ≥ 5% of the initial body weight has been lost, or the urinary concentration does not increase > 0.001 sp gr or > 30 mOsm/L in sequentially voided specimens. Serum electrolytes and osmolality are again determined, and 5 units of aqueous vasopressin are injected sc. Urine for sp gr or osmolality measurement is collected one final time 60 min postinjection, and the test is terminated.

A normal response produces maximum urine osmolality after dehydration (often > 1.020 sp gr or > 700 mOsm/L), exceeding the plasma osmolality; osmolality does not increase more than an additional 5% after injection of vasopressin. Patients with CDI are generally unable to concentrate urine to greater than the plasma osmolality but are able to increase their urine osmolality by > 50% after vasopressin administration. Patients with partial CDI are often able to concentrate urine to above the plasma osmolality but show a rise in urine osmolality of > 9% after vasopressin administration. Patients with NDI are unable to concentrate urine to greater than the plasma osmolality and show no additional response to vasopressin administration.

Measurement of circulating ADH is the most direct method of diagnosing CDI; levels at the end of the water deprivation test (before the vasopressin injection) are low in CDI and appropriately elevated in NDI. However, ADH levels are difficult to measure, and the test is not routinely available. In addition, water deprivation is so accurate that direct measurement of ADH is unnecessary. Plasma ADH levels are diagnostic after either dehydration or infusion of hypertonic saline.

Psychogenic polydipsia: Psychogenic polydipsia may present a difficult problem in differential diagnosis. Patients may ingest and excrete up to 6 L of fluid/day and are often emotionally disturbed. Unlike patients with CDI and NDI, they usually do not have nocturia, nor does their thirst wake them at night. Continued ingestion of large volumes of water in this situation can lead to life-threatening hyponatremia (see p. 823).

Patients with acute psychogenic water drinking are able to concentrate their urine during water deprivation. However, because chronic water intake diminishes medullary tonicity in the kidney, patients with longstanding polydipsia are not able to concentrate their urine to maximal levels during water deprivation, a response similar to that of patients with partial CDI. However, unlike CDI, patients with psychogenic polydipsia show no response to exogenous ADH after water deprivation. This response resembles NDI, except that basal ADH levels are low compared with the elevated levels present in NDI. After prolonged restriction of fluid intake to ≤ 2 L/day, normal concentrating ability returns within several weeks.

Treatment

• Desmopressin

CDI can be treated with hormone replacement and treatment of any correctable cause. In the absence of appropriate management, permanent renal damage can result.

Desmopressin, a synthetic analog of ADH with minimal vasoconstrictive properties, has prolonged antidiuretic activity lasting for 12 to 24 h in most patients and may be administered intranasally, sc, IV, or orally. Desmopressin is the preparation of choice for both adults and children and is available as an intranasal solution in 2 forms. A dropper bottle with a calibrated nasal catheter has the advantage of delivering incremental doses from 5 to 20 µg but is awkward to use. A spray bottle that delivers 10 µg of desmopressin in 0.1 mL of fluid is easier to use but delivers a fixed quantity. For each patient, the duration of action of a given dose must be established, because variation among individuals is great. The duration of action can be established by following timed urine volumes and osmolality. The nightly dose is the lowest dose required to prevent nocturia. The morning and evening doses should be adjusted separately. The usual dosage range in adults is 10 to 40 µg, with most adults requiring 10 µg bid. For children age 3 mo to 12 yr, the usual dosage range is 2.5 to 10 µg bid. Overdosage can lead to fluid retention and decreased plasma osmolality, possibly resulting in seizures in small children. In such instances, furosemide can be given to induce diuresis. Headache may be a troublesome adverse effect but generally disappears if the dosage is reduced. Infrequently, desmopressin causes a slight increase in BP. Absorption from the nasal mucosa may be erratic, especially when URI or allergic rhinitis occurs. When intranasal delivery of desmopressin is inappropriate, it may be administered sc using about one tenth the intranasal dose. Desmopressin may be used IV if a rapid effect is necessary (eg, for hypovolemia). With oral desmopressin, dose equivalence with the intranasal formulation is unpredictable, so individual dose titration is needed. The initial dose is 0.1 mg po tid, and the maintenance dose is usually 0.1 to 0.2 mg tid.

Lypressin (lysine-8-vasopressin), a synthetic agent, is given by nasal spray at doses of 2 to 4 units (7.5 to 15 µg) q 3 to 8 h but, because of its short duration of action, has been largely replaced by desmopressin.

Aqueous vasopressin 5 to 10 units sc or IM can be given to provide an antidiuretic response that usually lasts ≤ 6 h. Thus, this drug has little use in long-term treatment but can be used in the initial therapy of unconscious patients and in patients with CDI who are undergoing surgery. Synthetic vasopressin can also be administered bid to qid as a nasal spray, with the dosage and interval tailored to each patient. Vasopressin tannate in oil 0.3 to 1 mL (1.5 to 5 units) IM may control symptoms for up to 96 h.

At least 3 groups of nonhormonal drugs are useful in reducing polyuria: various diuretics, primarily thiazides; ADH-releasing drugs, such as chlorpropamide, carbamazepine, and clofibrate; and prostaglandin inhibitors, which are modestly effective. These drugs have been particularly useful in partial CDI and do not cause the adverse effects of exogenous ADH.

The thiazides paradoxically reduce urine volume in partial and complete CDI (and NDI), primarily as a consequence of reducing ECF volume and increasing proximal tubular resorption. Urine volumes may fall by 25 to 50% with 15 to 25 mg/kg of chlorothiazide. Restricting salt intake may also help because it reduces urine output by reducing solute load.

Chlorpropamide, carbamazepine, and clofibrate can reduce or eliminate the need for vasopressin in some patients with partial CDI. None are effective in NDI. Chlorpropamide (3 to 5 mg/kg po once/day or bid) causes some release of ADH and also potentiates the action of ADH on the kidney. Clofibrate (500 to 1000 mg po bid) or carbamazepine (100 to 400 mg po bid) is recommended for adults only. These drugs may be used synergistically with a diuretic. However, significant hypoglycemia may result from chlorpropamide.

Prostaglandin inhibitors (such as indomethacin 0.5 to 1.0 mg/kg po tid, although most NSAIDs are effective) may reduce urine volume, but generally by no more than 10 to 25%, perhaps by decreasing renal blood flow and GFR. Together with indomethacin, restriction of Na intake and a thiazide diuretic help further reduce urine volume in NDI.

Chapter 93. Thyroid Disorders

Introduction

The thyroid gland, located in the anterior neck just below the cricoid cartilage, consists of 2 lobes connected by an isthmus. Follicular cells in the gland produce the 2 main thyroid hormones, tetraiodothyronine (thyroxine, T_4) and triiodothyronine (T_3). These hormones act on cells in virtually every body tissue by combining with nuclear receptors and altering expression of a wide range of gene products. Thyroid hormone is required for normal brain and somatic tissue development in the fetus and neonate, and, in people of all ages, regulates protein, carbohydrate, and fat metabolism.

T_3 is the most active form; T_4 has only minimal hormonal activity. However, T_4 is much longer lasting and can be converted to T_3 (in most tissues) and thus serves as a reservoir for T_3. A 3rd form of thyroid hormone, reverse T_3 (rT_3), has no metabolic activity; levels of rT_3 increase in certain diseases.

Additionally, parafollicular cells (C cells) secrete the hormone calcitonin, which is released in response to hypercalcemia and lowers serum Ca levels (see p. 838).

Synthesis and Release of Thyroid Hormones

Synthesis of thyroid hormones requires iodine (see Fig. 93-1). Iodine, ingested in food and water as iodide, is actively concentrated by the thyroid and converted to organic iodine (organification) within follicular cells by thyroid peroxidase. The follicular cells surround a space filled with colloid, which consists of thyroglobulin, a glycoprotein containing tyrosine within its matrix. Tyrosine in contact with the membrane of the follicular cells is iodinated at 1 (monoiodotyrosine) or 2 (diiodotyrosine) sites and then coupled to produce the 2 forms of thyroid hormone (diiodotyrosine + diiodotyrosine → T_4; diiodotyrosine + monoiodotyrosine → T_3).

[**Fig. 93-1.** Synthesis of thyroid hormones.]

T_3 and T_4 remain incorporated in thyroglobulin within the follicle until the follicular cells take up thyroglobulin as colloid droplets. Once inside the thyroid follicular cells, T_3 and T_4 are cleaved from thyroglobulin. Free T_3 and T_4 are then released into the bloodstream, where they are bound to serum proteins for transport, the major one being thyroxine-binding globulin (TBG), which has high affinity but low capacity for T_3 and T_4. TBG normally carries about 75% of bound thyroid hormones. The other binding proteins are thyroxine-binding prealbumin (transthyretin), which has high affinity but low capacity for T_4, and albumin, which has low affinity but high capacity for T_3 and T_4. About 0.3% of total serum T_3 and 0.03% of total serum T_4 are free and in equilibrium with bound hormones. Only free T_3 and free T_4 are available to act on the peripheral tissues.

All reactions necessary for the formation and release of T_3 and T_4 are controlled by thyroid-stimulating hormone (TSH), which is secreted by pituitary thyrotropic cells. TSH secretion is controlled by a negative feedback mechanism in the pituitary: Increased levels of free T_4 and T_3 inhibit TSH synthesis and secretion, whereas decreased levels increase TSH secretion. TSH secretion is also influenced by thyrotropin-releasing hormone (TRH), which is synthesized in the hypothalamus. The precise mechanisms regulating TRH synthesis and release are unclear, although negative feedback from thyroid hormones inhibits TRH synthesis.

Most circulating T_3 is produced outside the thyroid by monodeiodination of T_4. Only one fifth of circulating T_3 is secreted directly by the thyroid.

Laboratory Testing of Thyroid Function

TSH measurement is the best means of determining thyroid dysfunction (see Table 93-1). Normal results essentially rule out hyperthyroidism or hypothyroidism, except in rare patients

with pituitary resistance to thyroid hormone or with central hypothyroidism due to disease in the hypothalamus, pituitary gland, or both. Serum TSH can be falsely low in very sick people. The serum TSH level also defines the syndromes of subclinical hyperthyroidism (low serum TSH) and subclinical hypothyroidism (elevated serum TSH), both

[**Table 93-1.** Results of Thyroid Function Tests in Various Clinical Situations]

of which are characterized by normal serum T_4, free T_4, serum T_3, and free T_3 levels.

Total serum T_4 is a measure of bound and free hormone. Changes in levels of thyroid hormone-binding serum proteins produce corresponding changes in total T_4, even though levels of physiologically active free T_4 are unchanged. Thus, a patient may be physiologically normal but have an abnormal total serum T_4 level. Free T_4 in the serum can be measured directly, avoiding the pitfalls of interpreting total T_4 levels.

Free T_4 index is a calculated value that corrects total T_4 for the effects of varying amounts of thyroid hormone-binding serum proteins and thus gives an estimate of free T_4 when total T_4 is measured. The thyroid hormone-binding ratio or T_3 resin uptake is used to estimate protein binding. Free T_4 index is readily available and compares well with direct measurement of free T_4.

Total serum T_3 and free T_3 can also be measured. Because T_3 is tightly bound to TBG (although 10 times less so than T_4), total serum T_3 levels are influenced by alterations in serum TBG level and by drugs that affect binding to TBG. Free T_3 levels in the serum are measured by the same direct and indirect methods (free T_3 index) described for T_4 and are used mainly for evaluating thyrotoxicosis.

TBG can be measured; it is increased in pregnancy, by estrogen therapy or oral contraceptive use, and in the acute phase of infectious hepatitis. TBG may also be increased by an X-linked abnormality. It is most commonly decreased by illnesses that reduce hepatic protein synthesis, use of anabolic steroids, and excessive corticosteroid use. Large doses of certain drugs, such as phenytoin and aspirin and their derivatives, displace T_4 from its binding sites on TBG, which spuriously lowers total serum T_4 levels.

Autoantibodies to thyroid peroxidase are present in almost all patients with Hashimoto's thyroiditis (some of whom also have autoantibodies to thyroglobulin) and in most patients with Graves' disease. These autoantibodies are markers of autoimmune disease but probably do not cause disease. However, an autoantibody directed against the TSH receptor on the thyroid follicular cell is responsible for the hyperthyroidism in Graves' disease. Antibodies against T_4 and T_3 may be found in patients with autoimmune thyroid disease and may affect T_4 and T_3 measurements but are rarely clinically significant.

The thyroid is the only source of thyroglobulin, which is readily detectable in the serum of healthy people and is usually elevated in patients with nontoxic or toxic goiter. The principal use of serum thyroglobulin measurement is in evaluating patients after near-total or total thyroidectomy (with or without ^{131}I ablation) for differentiated thyroid cancer. Normal or elevated serum thyroglobulin values indicate the presence of residual normal or cancerous thyroid tissue in patients receiving TSH-suppressive doses of L-thyroxine or after withdrawal of L-thyroxine. However, thyroglobulin antibodies can interfere with thyroglobulin measurement.

Radioactive iodine uptake can be measured. A trace amount of radioiodine is given orally or IV; a scanner then detects the amount of radioiodine taken up by the thyroid. The preferred radioiodine isotope is ^{123}I, which exposes the patient to minimal radiation (much less than ^{131}I). Thyroid ^{123}I uptake varies widely with iodine ingestion and is low in patients exposed to excess iodine.

The test is valuable in the differential diagnosis of hyperthyroidism (high uptake in Graves' disease, low uptake in thyroiditis—see p. 782). It may also help in the calculation of the dose of ^{131}I needed for treatment of hyperthyroidism.

Imaging by a scintillation camera can be done after radioisotope administration (radioiodine or technetium 99m pertechnetate) to produce a graphic representation of isotope uptake. Focal areas of increased (hot) or decreased (cold) uptake help distinguish areas of possible cancer (thyroid cancers exist in < 1% of hot nodules compared with 10 to 20% of cold nodules).

Screening: Screening every 5 yr by measuring serum TSH is recommended for all men ≥ 65 and for all women ≥ 35. For those with risk factors for thyroid disease, the serum TSH should be checked more often. Screening for hypothyroidism is as cost effective as screening for hypertension, hypercholesterolemia, and breast cancer. This single test is highly sensitive and specific in diagnosing or excluding two prevalent and serious disorders (hypothyroidism and hyperthyroidism), both of which can be treated effectively. Because of the high incidence of hypothyroidism in older people, screening on an annual basis is reasonable for those > age 70.

Approach to the Patient With a Thyroid Nodule

Thyroid nodules are common, increasingly so with increasing age. The reported incidence varies with the method of assessment. In middle-aged and elderly patients, palpation reveals nodules in about 5%. Results of ultrasonography and autopsy studies suggest that nodules are present in about 50% of adults. Many nodules are found incidentally on thyroid imaging studies done for other disorders.

Etiology

Most nodules are benign. Benign causes include hyperplastic colloid goiter, thyroid cysts, thyroiditis, and thyroid adenomas. Malignant causes include thyroid cancers (see p. 789).

Evaluation

History: Pain suggests thyroiditis or hemorrhage into a cyst. An asymptomatic nodule may be malignant but is usually benign. Symptoms of hyperthyroidism suggest a hyperfunctioning adenoma or thyroiditis, whereas symptoms of hypothyroidism suggest Hashimoto's thyroiditis. Risk factors for thyroid cancer include

- History of thyroid irradiation, especially in infancy or childhood
- Age < 20 yr
- Male sex
- Family history of thyroid cancer or multiple endocrine neoplasia
- A solitary nodule
- Dysphagia
- Dysphonia
- Increasing size (particularly rapid growth or growth while receiving thyroid suppression treatment)

Physical examination: Signs that suggest thyroid cancer include stony hard consistency or fixation to surrounding structures, cervical lymphadenopathy, and hoarseness due to recurrent laryngeal nerve paralysis.

Testing: Initial evaluation of a thyroid nodule consists of measurement of levels of

- Thyroid-stimulating hormone (TSH)
- Free thyroxine (T_4)

• Antithyroid peroxidase antibodies

If TSH is suppressed, radioiodine scanning is done. Nodules with increased radionuclide uptake (hot) are seldom malignant. If thyroid function tests do not indicate hyperthyroidism or Hashimoto's thyroiditis, or if nodules are indeterminate or cold, fine-needle aspiration biopsy is done to distinguish benign from malignant nodules. Early use of fine-needle aspiration biopsy is a more economic approach than routine use of radioiodine scans. Ultrasonography is useful in determining the size of the nodule but is rarely diagnostic of cancer, although cancer is suggested by ultrasonographic or x-ray evidence of fine, stippled, psammomatous calcification (papillary carcinoma) or dense, homogeneous calcification (medullary carcinoma). Fine-needle aspiration biopsy is not routinely indicated for nodules < 1 cm on ultrasonography.

Treatment

Treatment is directed at the underlying disorder. Thyroxine suppression of TSH to shrink smaller benign nodules is effective in no more than half the cases.

Euthyroid Sick Syndrome

Euthyroid sick syndrome is low serum levels of thyroid hormones in clinically euthyroid patients with nonthyroidal systemic illness. Diagnosis is based on excluding hypothyroidism. Treatment is of the underlying illness; thyroid hormone replacement is not indicated.

Patients with various acute or chronic nonthyroid disorders may have abnormal thyroid function tests. Such disorders include acute and chronic illness, particularly fasting, starvation, protein-energy undernutrition, major trauma, MI, chronic renal failure, diabetic ketoacidosis, anorexia nervosa, cirrhosis, thermal injury, and sepsis.

Decreased triiodothyronine (T_3) levels are most common. Patients with more severe or prolonged illness also have decreased thyroxine (T_4) levels. Serum reverse T_3 (rT_3) is increased. Patients are clinically euthyroid and do not have elevated thyroid-stimulating hormone (TSH) levels.

Pathogenesis is unknown but may include decreased peripheral conversion of T_4 to T_3, decreased clearance of rT_3 generated from T_4, and decreased binding of thyroid hormones to thyroxine-binding globulin (TBG). Proinflammatory cytokines (eg, tumor necrosis factor-α, IL-1) may be responsible for some changes.

Interpretation of abnormal thyroid function test results in ill patients is complicated by the effects of various drugs, including the iodine-rich contrast agents and amiodarone, which impairs the peripheral conversion of T_4 to T_3, and by drugs such as dopamine and corticosteroids, which decrease pituitary secretion of TSH, resulting in low serum TSH levels and subsequent decreased T_4 secretion.

Diagnosis

• TSH

• Serum cortisol

• Clinical judgment

The diagnostic dilemma is whether the patient has hypothyroidism or euthyroid sick syndrome. The best test is measurement of TSH, which in euthyroid sick syndrome is low, normal, or slightly elevated but not as high as it would be in hypothyroidism. Serum rT_3 is elevated, although this measurement is rarely done. Serum cortisol is often elevated in euthyroid sick syndrome and low or low-normal in hypothyroidism due to pituitary-hypothalamic disease. Because tests are nonspecific, clinical judgment is required to interpret abnormal thyroid function tests in the acutely or chronically ill patient. Unless thyroid

dysfunction is highly suspected, thyroid function tests should not be ordered for patients in the ICU.

Treatment

Treatment with thyroid hormone replacement is not appropriate. When the underlying disorder is treated, results of thyroid tests normalize.

Hashimoto's Thyroiditis

(Autoimmune Thyroiditis; Chronic Lymphocytic Thyroiditis; Hashimoto's Struma)

Hashimoto's thyroiditis is chronic autoimmune inflammation of the thyroid with lymphocytic infiltration. Findings include painless thyroid enlargement and symptoms of hypothyroidism. Diagnosis involves demonstration of high titers of thyroid peroxidase antibodies. Lifelong L-thyroxine replacement is typically required.

Hashimoto's thyroiditis is believed to be the most common cause of primary hypothyroidism in North America. It is twice as prevalent among women. Incidence increases with age and in patients with chromosomal disorders, including Down, Turner's, and Klinefelter's syndromes. A family history of thyroid disorders is common.

Hashimoto's thyroiditis, like Graves' disease, is sometimes associated with other autoimmune disorders, including Addison's disease (adrenal insufficiency), type 1 diabetes mellitus, hypoparathyroidism, vitiligo, premature graying of hair, pernicious anemia, connective tissue diseases (eg, RA, SLE, Sjogren's syndrome), and Schmidt's syndrome (Addison's disease, diabetes, and hypothyroidism secondary to Hashimoto's thyroiditis). There may be an increased incidence of thyroid tumors, rarely thyroid lymphoma. Pathologically, there is extensive infiltration of lymphocytes with lymphoid follicles and scarring.

Symptoms and Signs

Patients complain of painless enlargement of the thyroid or fullness in the throat. Examination reveals a nontender goiter that is smooth or nodular, firm, and more rubbery than the normal thyroid. Many patients present with symptoms of hypothyroidism, but some present with hyperthyroidism.

Diagnosis

• Thyroxine (T_4)

• Thyroid-stimulating hormone (TSH)

• Thyroid autoantibodies

Testing consists of measuring T_4, TSH, and thyroid autoantibodies; early in the disease T_4 and TSH levels are normal and there are high levels of thyroid peroxidase antibodies and less commonly of antithyroglobulin antibodies. Thyroid radioactive iodine uptake may be increased, perhaps because of defective iodide organification together with a gland that continues to trap iodine. Patients later develop hypothyroidism with decreased T_4, decreased thyroid radioactive iodine uptake, and increased TSH. Testing for other autoimmune disorders is warranted only when clinical manifestations are present.

Treatment

Occasionally, the hypothyroidism is transient, but most patients require lifelong thyroid hormone replacement, typically L-thyroxine 75 to 150 µg po once/day.

Hyperthyroidism

(Thyrotoxicosis)

Hyperthyroidism is characterized by hypermetabolism and elevated serum levels of free thyroid hormones. Symptoms are many but include tachycardia, fatigue, weight loss, nervousness, and tremor. Diagnosis is clinical and with thyroid function tests. Treatment depends on cause.

Hyperthyroidism can be classified on the basis of thyroid radioactive iodine uptake and the presence or absence of circulating thyroid stimulators (see Table 93-1).

Etiology

Hyperthyroidism may result from increased synthesis and secretion of thyroid hormones (thyroxine [T_4] and triiodothyronine [T_3]) from the thyroid, caused by thyroid stimulators in the blood or by autonomous thyroid hyperfunction. It can also result from excessive release of thyroid hormone from the thyroid without increased synthesis. Such release is commonly caused by the destructive changes of various types of thyroiditis. Various clinical syndromes also cause hyperthyroidism.

Graves' disease (toxic diffuse goiter), the most common cause of hyperthyroidism, is characterized by hyperthyroidism and one or more of the following:

• Goiter

• Exophthalmos

• Infiltrative dermopathy

Graves' disease is caused by an autoantibody against the thyroid receptor for thyroid-stimulating hormone (TSH); unlike most autoantibodies, which are inhibitory, this autoantibody is stimulatory, thus causing continuous synthesis and secretion of excess T_4 and T_3. Graves' disease (like Hashimoto's thyroiditis) sometimes occurs with other autoimmune disorders, including type 1 diabetes mellitus, vitiligo, premature graying of hair, pernicious anemia, connective tissue diseases, and polyglandular deficiency syndrome. The pathogenesis of infiltrative ophthalmopathy (responsible for the exophthalmos in Graves' disease) is poorly understood but may result from immunoglobulins directed to specific receptors in the orbital fibroblasts and fat that result in release of proinflammatory cytokines, inflammation, and accumulation of glycosaminoglycans. Ophthalmopathy may also occur before the onset of hyperthyroidism or as late as 20 yr afterward and frequently worsens or abates independently of the clinical course of hyperthyroidism. Typical ophthalmopathy in the presence of normal thyroid function is called euthyroid Graves' disease.

Inappropriate TSH secretion is a rare cause. Patients with hyperthyroidism have essentially undetectable TSH except for those with a TSH-secreting anterior pituitary adenoma or pituitary resistance to thyroid hormone. TSH levels are high, and the TSH produced in both disorders is biologically more active than normal TSH. An increase in the α-subunit of TSH in the blood (helpful in differential diagnosis) occurs in patients with a TSH-secreting pituitary adenoma.

Molar pregnancy, choriocarcinoma, and hyperemesis gravidarum produce high levels of serum human chorionic gonadotropin (hCG), a weak thyroid stimulator. Levels of hCG are highest during the 1st trimester of pregnancy and result in the decrease in serum TSH and mild increase in serum free T_4 sometimes observed at that time. The increased thyroid stimulation may be caused by increased levels of partially desialated hCG, an hCG variant that seems to be a more potent thyroid stimulator than more sialated hCG. Hyperthyroidism in molar pregnancy, choriocarcinoma, and hyperemesis gravidarum is transient; normal thyroid function resumes when the molar pregnancy is evacuated, the choriocarcinoma is appropriately treated, or the hyperemesis gravidarum abates.

Nonautoimmune autosomal dominant hyperthyroidism manifests during infancy. It results from mutations in the TSH receptor gene that produce continuous thyroid stimulation.

Toxic solitary or multinodular goiter (Plummer's disease) sometimes results from TSH receptor gene mutations producing continuous thyroid stimulation. Patients with toxic nodular goiter have none of the autoimmune manifestations or circulating antibodies observed in patients with Graves' disease. Also, in contrast to Graves' disease, toxic solitary and multinodular goiters usually do not remit.

Inflammatory thyroid disease (thyroiditis) includes subacute granulomatous thyroiditis, Hashimoto's thyroiditis, and silent lymphocytic thyroiditis, a variant of Hashimoto's thyroiditis (see p. 787). Hyperthyroidism results from destructive changes in the gland and release of stored hormone, not from increased synthesis. Hypothyroidism may follow.

Drug-induced hyperthyroidism can result from amiodarone and interferon alfa, which may induce thyroiditis with hyperthyroidism and other thyroid disorders. Although more commonly causing hypothyroidism, lithium can rarely cause hyperthyroidism. Patients receiving these drugs should be closely monitored.

Thyrotoxicosis factitia is hyperthyroidism resulting from conscious or accidental overingestion of thyroid hormone.

Excess iodine ingestion causes hyperthyroidism with a low thyroid radioactive iodine uptake. It most often occurs in patients with underlying nontoxic nodular goiter (especially elderly patients) who are given drugs that contain iodine (eg, amiodarone, iodine-containing expectorants) or who undergo radiologic studies using iodine-rich contrast agents. The etiology may be that the excess iodine provides substrate for functionally autonomous (ie, not under TSH regulation) areas of the thyroid to produce hormone. Hyperthyroidism usually persists as long as excess iodine remains in the circulation.

Metastatic thyroid cancer is a possible cause. Overproduction of thyroid hormone occurs rarely from functioning metastatic follicular carcinoma, especially in pulmonary metastases.

Struma ovarii develops when ovarian teratomas contain enough thyroid tissue to cause true hyperthyroidism. Radioactive iodine uptake occurs in the pelvis, and uptake by the thyroid is usually suppressed.

Pathophysiology

In hyperthyroidism, serum T_3 usually increases more than does T_4, probably because of increased secretion of T_3 as well as conversion of T_4 to T_3 in peripheral tissues. In some patients, only T_3 is elevated (T_3 toxicosis). T_3 toxicosis may occur in any of the usual disorders that cause hyperthyroidism, including Graves' disease, multinodular goiter, and the autonomously functioning solitary thyroid nodule. If T_3 toxicosis is untreated, the patient usually also develops laboratory abnormalities typical of hyperthyroidism (ie, elevated T_4 and ^{123}I uptake). The various forms of thyroiditis commonly have a hyperthyroid phase followed by a hypothyroid phase.

Symptoms and Signs

Most symptoms and signs are the same regardless of the cause. Exceptions include infiltrative ophthalmopathy and dermopathy, which occur only in Graves' disease.

The clinical presentation may be dramatic or subtle. A goiter or nodule may be present. Many common symptoms and signs of hyperthyroidism are similar to those of adrenergic excess, such as nervousness, palpitations, hyperactivity, increased sweating, heat hypersensitivity, fatigue, increased appetite, weight loss, insomnia, weakness, and frequent bowel movements (occasionally diarrhea). Hypomenorrhea may be present. Signs may include warm, moist skin; tremor; tachycardia; widened pulse pressure; atrial fibrillation; and palpitations.

Elderly patients, particularly those with toxic nodular goiter, may present atypically (apathetic or masked hyperthyroidism) with symptoms more akin to depression or dementia. Most do not have exophthalmos or tremor. Atrial fibrillation, syncope, altered sensorium, heart failure, and weakness are more likely.

Symptoms and signs may involve only a single organ system.

Eye signs include stare, eyelid lag, eyelid retraction, and mild conjunctival injection and are largely due to excessive adrenergic stimulation. They usually remit with successful treatment. Infiltrative ophthalmopathy, a more serious development, is specific to Graves' disease and can occur years before or after hyperthyroidism. It is characterized by orbital pain, lacrimation, irritation, photophobia, increased retro-orbital tissue, exophthalmos, and lymphocytic infiltration of the extraocular muscles, causing ocular muscle weakness that frequently leads to double vision.

Infiltrative dermopathy, also called pretibial myxedema (a confusing term, because myxedema suggests hypothyroidism), is characterized by nonpitting infiltration by proteinaceous ground substance, usually in the pretibial area. It rarely occurs in the absence of Graves' ophthalmopathy. The lesion is often pruritic and erythematous in its early stages and subsequently becomes brawny. Infiltrative dermopathy may appear years before or after hyperthyroidism.

Thyroid storm: Thyroid storm is an acute form of hyperthyroidism that results from untreated or inadequately treated severe hyperthyroidism. It is rare, occurring in patients with Graves' disease or toxic multinodular goiter (a solitary toxic nodule is less common and generally less severe). It may be precipitated by infection, trauma, surgery, embolism, diabetic ketoacidosis, or preeclampsia. Thyroid storm causes abrupt florid symptoms of hyperthyroidism with one or more of the following: fever, marked weakness and muscle wasting, extreme restlessness with wide emotional swings, confusion, psychosis, coma, nausea, vomiting, diarrhea, and hepatomegaly with mild jaundice. The patient may present with cardiovascular collapse and shock. *Thyroid storm is a life-threatening emergency requiring prompt treatment.*

Diagnosis

• TSH

• Free T_4

• Sometimes radioactive iodine uptake

Diagnosis is based on history, physical examination, and thyroid function tests. Serum TSH measurement is the best test, because TSH is suppressed in hyperthyroid patients except in the rare instance when the etiology is a TSH-secreting pituitary adenoma or pituitary resistance to thyroid hormone. Screening selected populations for TSH level is warranted (see p. 776). Free T_4 is increased in hyperthyroidism. However, T_4 can be falsely normal in true hyperthyroidism in patients with a severe systemic illness (similar to the falsely low levels that occur in euthyroid sick syndrome) and in T_3 toxicosis. If free T_4 level is normal and TSH is low in a patient with subtle symptoms and signs of hyperthyroidism, then serum T_3 should be measured to detect T_3 toxicosis; an elevated level confirms that diagnosis.

The cause can often be diagnosed clinically (eg, exposure to a drug, the presence of signs specific to Graves' disease). If not, thyroid radioactive iodine uptake may be obtained by using ^{123}I. When hyperthyroidism is due to hormone overproduction, thyroid radioactive iodine uptake is usually elevated.

TSH receptor antibodies can be measured to detect Graves' disease, but measurement is rarely necessary except during the 3rd trimester of pregnancy to assess the risk of neonatal Graves' disease; TSH receptor antibodies readily cross the placenta to stimulate the fetal thyroid. Most patients with Graves' disease have circulating antithyroid peroxidase antibodies, and fewer have antithyroglobulin antibodies.

Inappropriate TSH secretion is uncommon. The diagnosis is confirmed when hyperthyroidism occurs with elevated circulating free T_4 and T_3 concentrations and normal or elevated serum TSH.

If thyrotoxicosis factitia is suspected, serum thyroglobulin can be measured; it is usually low or low-normal

—unlike in all other causes of hyperthyroidism.

In hyperthyroidism caused by excess iodine ingestion, low radioactive iodine uptake is typical because thyroid radioactive iodine uptake is inversely proportional to iodine intake.

Treatment

Treatment depends on cause but may include

• Propylthiouracil or methimazole

• β-Blockers

• Iodine

• Radioactive iodine

• Surgery

Iodine: Iodine in pharmacologic doses inhibits the release of T_3 and T_4 within hours and inhibits the organification of iodine, a transitory effect lasting from a few days to a week, after which inhibition usually ceases. Iodine is used for emergency management of thyroid storm, for hyperthyroid patients undergoing emergency nonthyroid surgery, and (because it also decreases the vascularity of the thyroid) for preoperative preparation of hyperthyroid patients undergoing subtotal thyroidectomy. Iodine generally is not used for routine treatment of hyperthyroidism. The usual dosage is 2 to 3 drops (100 to 150 mg) of a saturated K iodide solution po tid or qid or 0.5 to 1 g Na iodide in 1 L 0.9% saline solution given IV slowly q 12 h.

Complications of iodine therapy include inflammation of the salivary glands, conjunctivitis, and rash.

Propylthiouracil and methimazole: These antithyroid drugs block thyroid peroxidase, decreasing the organification of iodide, and impair the coupling reaction. Propylthiouracil in high doses also inhibits the peripheral conversion of T_4 to T_3. About 20 to 50% of patients with Graves' disease remain in remission after a 1- to 2-yr course of either drug. The return to normal or a marked decrease in gland size, the restoration of a normal serum TSH level, and less severe hyperthyroidism before therapy are good prognostic signs of long-term remission. The concomitant use of antithyroid drug therapy and L-thyroxine does not improve the remission rate in patients with Graves' disease. Because toxic nodular goiter rarely goes into remission, antithyroid drug therapy is given only in preparation for surgical treatment or ^{131}I therapy.

The usual starting dosage of propylthiouracil is 100 to 150 mg po q 8 h and of methimazole 5 to 20 mg po tid. When T_4 and T_3 levels normalize, the dosage is decreased to the lowest effective amount, usually propylthiouracil 50 mg tid or methimazole 5 to 15 mg once/day. Usually, control is achieved in 2 to 3 mo. More rapid control can be achieved by increasing the dosage of propylthiouracil to 150 to 200 mg q 8 h. Such dosages or higher ones (up to 400 mg q 8 h) are generally reserved for severely ill patients, including those with thyroid storm. Maintenance doses can be continued for one or many years depending on the clinical circumstances. Carbimazole, which is used widely in Europe, is rapidly converted to methimazole. The usual starting dose is similar to that of methimazole; maintenance dosage is 5 to 20 mg po once/day, 2.5 to 10 mg bid, or 1.7 to 6.7 mg tid.

Adverse effects include rash, allergic reactions, abnormal liver function, and, in about 0.1% of patients, reversible agranulocytosis. Patients allergic to one drug can be switched to the other, but cross-sensitivity may occur. If agranulocytosis occurs, the patient cannot be switched to the other drug; other therapy (eg, radioiodine, surgery) should be used.

Each drug has advantages and disadvantages. Methimazole need only be given once/day, which improves adherence. Furthermore, when methimazole is used in dosages of < 40 mg/day, agranulocytosis

is less common; with propylthiouracil, agranulocytosis may occur at any dosage. Propylthiouracil may be preferred if antithyroid drugs must be used during pregnancy or breastfeeding because it is less likely to cross the placenta or enter breast milk. Methimazole has been used successfully in pregnant and nursing women without fetal or infant complications, but rarely methimazole has been associated with scalp and GI defects in the neonate. Propylthiouracil is also preferred for the treatment of thyroid storm, because the dosages used (800 to 1200 mg/day) partially block the peripheral conversion of T_4 to T_3.

The combination of high-dose propylthiouracil and dexamethasone, also a potent inhibitor of T_4 to T_3 conversion, can relieve symptoms of hyperthyroidism and restore the serum T_3 level to normal within a week.

β-Blockers: Symptoms and signs of hyperthyroidism due to adrenergic stimulation may respond to β-blockers; propranolol has had the greatest use, but atenolol or metoprolol may be preferable.

Other manifestations typically do not respond.

- Manifestations typically responding to β-blockers: Tachycardia, tremor, mental symptoms, eyelid lag; occasionally heat intolerance and sweating, diarrhea, proximal myopathy

- Manifestations typically not responding to β-blockers: O_2 consumption, exophthalmos, goiter, bruit, circulating thyroxine levels, weight loss

Propranolol is indicated in thyroid storm (see Table 93-2). It rapidly decreases heart rate, usually within 2 to 3 h when given orally and within minutes when given IV. Esmolol may be used in the ICU because it requires careful titration and monitoring. Propranolol is also indicated for tachycardia with hyperthyroidism, especially in elderly patients, because antithyroid drugs usually take several weeks to become fully effective. Ca channel blockers may control tachyarrhythmias in patients in whom β-blockers are contraindicated.

Radioactive sodium iodine (^{131}I, radioiodine): In the US, ^{131}I is the most common treatment for hyperthyroidism. Radioiodine is often recommended as the treatment of choice for

[**Table 93-2.** Treatment of Thyroid Storm]

Graves' disease and toxic nodular goiter in all patients, including children. Dosage of ^{131}I is difficult to adjust because the response of the gland cannot be predicted; some physicians give a standard dose of 8 to 10 mCi. Others adjust the dose based on estimated thyroid size and the 24-h uptake to provide a dose of 80 to 120 μCi/g thyroid tissue.

When sufficient ^{131}I is given to cause euthyroidism, about 25% of patients become hypothyroid 1 yr later, and the incidence continues to increase yearly. Thus, most patients eventually become hypothyroid. However, if smaller doses are used, incidence of recurrence is higher. Larger doses, such as 10 to 15 mCi, often cause hypothyroidism within 6 mo.

Radioactive iodine is not used during pregnancy. There is no proof that radioiodine increases the incidence of tumors, leukemia, thyroid cancer, or birth defects in children born to women who become pregnant later in life.

Surgery: Surgery is indicated for patients with Graves' disease whose hyperthyroidism has recurred after courses of antithyroid drugs and who refuse ^{131}I therapy, patients who cannot tolerate antithyroid drugs, patients with very large goiters, and in some younger patients with toxic adenoma and multinodular goiter. Surgery may be done in elderly patients with giant nodular goiters.

Surgery usually restores normal function. Postoperative recurrences vary between 2 and 16%; risk of hypothyroidism is directly related to the extent of surgery and occurs in about one half of patients. Vocal cord paralysis and hypoparathyroidism are uncommon complications. Saturated solution of K iodide 3

drops (about 100 to 150 mg) po tid should be given for 10 days before surgery to reduce the vascularity of the gland. Propylthiouracil or methimazole must also be given, because the patient should be euthyroid before iodide is given. Dexamethasone can be added to rapidly restore euthyroidism. Surgical procedures are more difficult in patients who previously underwent thyroidectomy or radioiodine therapy.

Treatment of thyroid storm: A treatment regimen for thyroid storm is shown in Table 93-2.

Treatment of infiltrative dermopathy and ophthalmopathy: In infiltrative dermopathy (in Graves' disease), topical corticosteroids sometimes relieve the pruritus. Dermopathy usually remits spontaneously after months or years. Ophthalmopathy should be treated jointly by the endocrinologist and ophthalmologist and may require corticosteroids, orbital radiation, and surgery.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is low serum TSH in patients with normal serum free T_4 and T_3 and absent or minimal symptoms of hyperthyroidism.

Subclinical hyperthyroidism is far less common than subclinical hypothyroidism (see p. 787). Patients with serum TSH < 0.1 mU/L have an increased incidence of atrial fibrillation (particularly elderly patients), reduced bone mineral density, increased fractures, and increased mortality. Patients with serum TSH that is only slightly below normal are less likely to have these features. Many patients with subclinical hyperthyroidism are taking L-thyroxine; in these patients, reduction of the dose is the most appropriate management unless therapy is aimed at maintaining a suppressed TSH in patients with thyroid cancer or nodules. The other causes of subclinical hyperthyroidism are the same as those for clinically apparent hyperthyroidism.

Therapy is indicated for patients with endogenous subclinical hyperthyroidism (serum TSH < 0.1 mU/L), especially those with atrial fibrillation or reduced bone mineral density. The usual treatment is ^{131}I. In patients with milder symptoms (eg, nervousness), a trial of antithyroid drug therapy is worthwhile.

Hypothyroidism

(Myxedema)

Hypothyroidism is thyroid hormone deficiency. It is diagnosed by clinical features such as a typical facies, hoarse slow speech, and dry skin and by low levels of thyroid hormones. Management includes treatment of the cause and administration of thyroxine.

Hypothyroidism occurs at any age but is particularly common among the elderly. It occurs in close to 10% of women and 6% of men > 65. Although typically easy to diagnose in younger adults, it may be subtle and manifest atypically in the elderly.

Primary hypothyroidism: Primary hypothyroidism is due to disease in the thyroid; thyroid-stimulating hormone (TSH) is increased. The most common cause is probably autoimmune. It usually results from Hashimoto's thyroiditis and is often associated with a firm goiter or, later in the disease process, with a shrunken fibrotic thyroid with little or no function. The 2nd most common cause is post-therapeutic hypothyroidism, especially after radioactive iodine therapy or surgery for hyperthyroidism or goiter. Hypothyroidism during overtreatment with propylthiouracil, methimazole, and iodide abates after therapy is stopped.

Most patients with non-Hashimoto's goiters are euthyroid or have hyperthyroidism, but goitrous hypothyroidism may occur in endemic goiter. Iodine deficiency decreases thyroid hormonogenesis. In response, TSH is released, which causes the thyroid to enlarge and trap iodine avidly; thus, goiter results. If iodine deficiency is severe, the patient becomes hypothyroid, a rare occurrence in the US since the advent of iodized salt.

Iodine deficiency can cause endemic cretinism in children; endemic cretinism is the most common cause

of congenital hypothyroidism in severely iodine-deficient regions and a major cause of mental deficiency worldwide.

Rare inherited enzymatic defects can alter the synthesis of thyroid hormone and cause goitrous hypothyroidism (see p. 2887).

Hypothyroidism may occur in patients taking lithium, perhaps because lithium inhibits hormone release by the thyroid. Hypothyroidism may also occur in patients taking amiodarone or other iodine-containing drugs, and in patients taking interferon alfa. Hypothyroidism can result from radiation therapy for cancer of the larynx or Hodgkin lymphoma (Hodgkin's disease). The incidence of permanent hypothyroidism after radiation therapy is high, and thyroid function (through measurement of serum TSH) should be evaluated at 6- to 12-mo intervals.

Secondary hypothyroidism: Secondary hypothyroidism occurs when the hypothalamus produces insufficient thyrotropin-releasing hormone (TRH) or the pituitary produces insufficient TSH. Sometimes, deficient TSH secretion due to deficient TRH secretion is termed tertiary hypothyroidism.

Symptoms and Signs

Symptoms and signs of primary hypothyroidism are often subtle and insidious. Symptoms may include cold intolerance, constipation, forgetfulness, and personality changes. Modest weight gain is largely the result of fluid retention and decreased metabolism. Paresthesias of the hands and feet are common, often due to carpal-tarsal tunnel syndrome caused by deposition of proteinaceous ground substance in the ligaments around the wrist and ankle. Women with hypothyroidism may develop menorrhagia or secondary amenorrhea.

The facial expression is dull; the voice is hoarse and speech is slow; facial puffiness and periorbital swelling occur due to infiltration with the mucopolysaccharides hyaluronic acid and chondroitin sulfate; eyelids droop because of decreased adrenergic drive; hair is sparse, coarse, and dry; and the skin is coarse, dry, scaly, and thick. The relaxation phase of deep tendon reflexes is slowed. Hypothermia is common. Dementia or frank psychosis (myxedema madness) may occur.

Carotenemia is common, particularly notable on the palms and soles, caused by deposition of carotene in the lipid-rich epidermal layers. Deposition of proteinaceous ground substance in the tongue may cause macroglossia. A decrease in both thyroid hormone and adrenergic stimulation causes bradycardia. The heart may be enlarged, partly because of dilation but chiefly because of pericardial effusion. Pleural or abdominal effusions also may be noted. The pericardial and pleural effusions develop slowly and only rarely cause respiratory or hemodynamic distress.

Elderly patients have significantly fewer symptoms than do younger adults, and complaints are often subtle and vague. Many elderly patients with hypothyroidism present with nonspecific geriatric syndromes —confusion, anorexia, weight loss, falling, incontinence, and decreased mobility. Musculoskeletal symptoms (especially arthralgias) occur often, but arthritis is rare. Muscular aches and weakness, often mimicking polymyalgia rheumatica or polymyositis, and an elevated CK level may occur. In the elderly, hypothyroidism may mimic dementia or parkinsonism.

Although secondary hypothyroidism is uncommon, its causes often affect other endocrine organs controlled by the hypothalamic-pituitary axis. In a woman with hypothyroidism, indications of secondary hypothyroidism are a history of amenorrhea rather than menorrhagia and some suggestive differences on physical examination. Secondary hypothyroidism is characterized by skin and hair that are dry but not very coarse, skin depigmentation, only minimal macroglossia, atrophic breasts, and low BP. Also, the heart is small, and serous pericardial effusions do not occur. Hypoglycemia is common because of concomitant adrenal insufficiency or growth hormone deficiency.

Myxedema coma: Myxedema coma is a life-threatening complication of hypothyroidism, usually occurring in patients with a long history of hypothyroidism. Its characteristics include coma with extreme hypothermia (temperature 24° to 32.2° C), areflexia, seizures, and respiratory depression with CO_2 retention. Severe hypothermia may be missed unless low-reading thermometers are used. Rapid

diagnosis based on clinical judgment, history, and physical examination is imperative, because death is likely without rapid treatment. Precipitating factors include illness, infection, trauma, drugs that suppress the CNS, and exposure to cold.

Diagnosis

• TSH

• Free thyroxine (T_4)

Serum TSH is the most sensitive test, and screening of selected populations is warranted (see p. 776). In primary hypothyroidism, there is no feedback inhibition of the intact pituitary, and serum TSH is always elevated, whereas serum free T_4 is low. In secondary hypothyroidism, free T_4 and serum TSH are low (sometimes TSH is normal but with decreased bioactivity).

Many patients with primary hypothyroidism have normal circulating levels of triiodothyronine (T_3), probably caused by sustained TSH stimulation of the failing thyroid, resulting in preferential synthesis and secretion of biologically active T_3. Therefore, serum T_3 is not sensitive for hypothyroidism.

Anemia is often present, usually normocytic-normochromic and of unknown etiology, but it may be hypochromic because of menorrhagia and sometimes macrocytic because of associated pernicious anemia or decreased absorption of folate. Anemia is rarely severe (Hb > 9 g/dL). As the hypometabolic state is corrected, anemia subsides, sometimes requiring 6 to 9 mo.

Serum cholesterol is usually high in primary hypothyroidism but less so in secondary hypothyroidism.

In addition to primary and secondary hypothyroidism, other conditions may cause decreased levels of total T_4, such as serum thyroxine-binding globulin (TBG) deficiency, some drugs (see p. 785), and euthyroid sick syndrome (see p. 779).

Treatment

• L-Thyroxine, adjusted until TSH levels are in midnormal range

Various thyroid hormone preparations are available for replacement therapy, including synthetic preparations of T_4 (L-thyroxine), T_3 (liothyronine), combinations of the 2 synthetic hormones, and desiccated animal thyroid extract. L-Thyroxine is preferred; the usual maintenance dose is 75 to 150 µg po once/day, depending on age, body mass index, and absorption (for pediatric doses, see p. 2888). Therapy is begun with low doses, especially in the elderly, usually 25 µg once/day. The dose is adjusted every 6 wk until maintenance dose is achieved. The maintenance dose may need to be decreased in elderly patients and increased in pregnant women. Dose may also need to be increased if drugs that decrease T_4 absorption or increase its biliary excretion are administered concomitantly. The dose used should be the lowest that restores serum TSH levels to the midnormal range (though this criterion cannot be used in patients with secondary hypothyroidism).

Liothyronine should not be used alone for long-term replacement because of its short half-life and the large peaks in serum T_3 levels it produces. The administration of standard replacement amounts (25 to 37.5 µg bid) results in rapidly increasing serum T_3 to between 300 and 1000 ng/dL (4.62 to 15.4 nmol/L) within 4 h due to its almost complete absorption; these levels return to normal by 24 h. Additionally, patients receiving liothyronine are chemically hyperthyroid for at least several hours a day, potentially increasing cardiac risks.

Similar patterns of serum T_3 occur when mixtures of T_3 and T_4 are taken po, although peak T_3 is lower because less T_3 is given. Replacement regimens with synthetic T_4 preparations reflect a different pattern in serum T_3 response. Increases in serum T_3 occur gradually, and normal levels are maintained when adequate doses of T_4 are given. Desiccated animal thyroid preparations contain variable amounts of T_3

and T_4 and should not be prescribed unless the patient is already taking the preparation and has normal serum TSH.

In patients with secondary hypothyroidism, L-thyroxine should not be given until there is evidence of adequate cortisol secretion (or cortisol therapy is given), because L-thyroxine could precipitate adrenal crisis.

Myxedema coma: Myxedema coma is treated as follows:

• T_4 given IV

• Corticosteroids

• Supportive care as needed

• Conversion to oral T_4 when patient is stable

Patients require a large initial dose of T_4 (300 to 500 µg IV) or T_3 (25 to 50 µg IV). The IV maintenance dose of T_4 is 75 to 100 µg once/day and of T_3, 10 to 20 µg bid until T_4 can be given orally. Corticosteroids are also given, because the possibility of central hypothyroidism usually cannot be initially ruled out. The patient should not be rewarmed rapidly, which may precipitate hypotension or arrhythmias. Hypoxemia is common, so PaO_2 should be monitored. If ventilation is compromised, immediate mechanical ventilatory assistance is required. The precipitating factor should be rapidly and appropriately treated and fluid replacement given carefully, because hypothyroid patients do not excrete water appropriately. Finally, all drugs should be given cautiously because they are metabolized more slowly than in healthy people.

Subclinical Hypothyroidism

Subclinical hypothyroidism is elevated serum TSH in patients with absent or minimal symptoms of hypothyroidism and normal serum levels of free T_4.

Subclinical thyroid dysfunction is relatively common; it occurs in more than 15% of elderly women and 10% of elderly men, particularly in those with underlying Hashimoto's thyroiditis.

In patients with serum TSH > 10 mU/L, there is a high likelihood of progression to overt hypothyroidism with low serum levels of free T_4 in the next 10 yr. These patients are also more likely to have hypercholesterolemia and atherosclerosis. They should be treated with L-thyroxine, even if they are asymptomatic. For patients with TSH levels between 4.5 and 10 mU/L, a trial of L-thyroxine is reasonable if symptoms of early hypothyroidism (eg, fatigue, depression) are present. L-Thyroxine therapy is also indicated in pregnant women and in women who plan to become pregnant to avoid deleterious effects of hypothyroidism on the pregnancy and fetal development. Patients should have annual measurement of serum TSH and free T_4 to assess progress of the condition if untreated or to adjust the L-thyroxine dosage.

Silent Lymphocytic Thyroiditis

Silent lymphocytic thyroiditis is a self-limited, subacute disorder occurring most commonly in women during the postpartum period. Symptoms are initially of hyperthyroidism, then hypothyroidism, and then generally recovery to the euthyroid state. Treatment of the hyperthyroid phase is with a β-blocker. If hypothyroidism is permanent, lifelong thyroxine supplementation is needed.

The term "silent" refers to the absence of thyroid tenderness in contrast with subacute thyroiditis, which usually causes thyroid tenderness. Silent lymphocytic thyroiditis causes most cases of postpartum thyroid dysfunction. It occurs in about 5 to 10% of postpartum women.

Thyroid biopsy reveals lymphocytic infiltration as in Hashimoto's thyroiditis but without lymphoid follicles and scarring. Thyroid peroxidase autoantibodies and, less commonly, antithyroglobulin antibodies are almost always positive during pregnancy and the postpartum period. Thus, this disorder would seem to be a variant of Hashimoto's thyroiditis (see p. 779).

Symptoms and Signs

The condition begins in the postpartum period, usually within 12 to 16 wk. Silent lymphocytic thyroiditis is characterized by a variable degree of painless thyroid enlargement with a hyperthyroid phase of several weeks, often followed by transient hypothyroidism due to depleted thyroid hormone stores but usually eventual recovery to the euthyroid state (as noted for painful subacute thyroiditis). The hyperthyroid phase is self-limited and may be brief or overlooked. Many women with this disorder are diagnosed when they become hypothyroid, which occasionally is permanent.

Diagnosis

• Clinical evaluation

• Serum thyroxine (T_4), triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) levels

Silent lymphocytic thyroiditis is frequently undiagnosed. Suspicion of the diagnosis generally depends on clinical findings, typically once hypothyroidism has occurred. Eye signs and pretibial myxedema do not occur.

Thyroid function test results vary depending on the phase of illness. Initially, serum T_4 and T_3 are elevated and TSH is suppressed. In the hypothyroid phase, these findings are reversed. WBC count and ESR are normal. Needle biopsy provides definitive diagnosis but is usually unnecessary.

Treatment

• Usually a β-blocker

• Sometimes thyroid hormone replacement

Because silent lymphocytic thyroiditis lasts only a few months, treatment is conservative, usually requiring only a β-blocker (eg, propranolol) during the hyperthyroid phase (see p. 783). Antithyroid drugs, surgery, and radioiodine therapy are contraindicated. Thyroid hormone replacement may be required during the hypothyroid phase. Most patients recover normal thyroid function, although some remain permanently hypothyroid. Therefore, thyroid function should be reevaluated after 9 to 12 mo of thyroxine therapy; replacement is stopped for 5 wk, and TSH is remeasured. This disorder usually recurs after subsequent pregnancies.

Subacute Thyroiditis

(de Quervain's Thyroiditis; Giant Cell Thyroiditis; Granulomatous Thyroiditis)

Subacute thyroiditis is an acute inflammatory disease of the thyroid probably caused by a virus. Symptoms include fever and thyroid tenderness. Initial hyperthyroidism is common, sometimes followed by a transient period of hypothyroidism. Diagnosis is clinical and with thyroid function tests. Treatment is with high doses of NSAIDs or with corticosteroids. The disease usually resolves spontaneously within months.

History of an antecedent viral URI is common. Histologic studies show less lymphocytic infiltration of the thyroid than in Hashimoto's thyroiditis or silent thyroiditis, but there is characteristic giant cell infiltration, PMNs, and follicular disruption.

Symptoms and Signs

There is pain in the anterior neck and fever of 37.8° to 38.3° C. Neck pain characteristically shifts from side to side and may settle in one area, frequently radiating to the jaw and ears. It is often confused with dental pain, pharyngitis, or otitis and is aggravated by swallowing or turning of the head. Symptoms of hyperthyroidism are common early in the disease because of hormone release from the disrupted follicles. There is more lassitude and prostration than in other thyroid disorders. On physical examination, the thyroid is asymmetrically enlarged, firm, and tender.

Diagnosis

• Clinical findings

• Free thyroxine (T_4) and thyroid-stimulating hormone (TSH) levels

• ESR

• Radioactive iodine uptake

Diagnosis is primarily clinical, based on finding an enlarged, tender thyroid in patients with the appropriate clinical history. Thyroid testing with TSH and at least a free T_4 measurement is usually also done. Radioactive iodine uptake should be measured to confirm the diagnosis. When the diagnosis is uncertain, finer needle aspiration biopsy is useful. Thyroid ultrasonography with color Doppler shows reduced blood flow in contrast with the increased flow of Graves' disease. Laboratory findings early in the disease include an increase in free T_4 and triiodothyronine (T_3), a marked decrease in TSH and thyroid radioactive iodine uptake (often 0), and a high ESR. After several weeks, the thyroid is depleted of T_4 and T_3 stores, and transient hypothyroidism develops accompanied by a decrease in free T_4 and T_3, a rise in TSH, and recovery of thyroid radioactive iodine uptake. Weakly positive thyroid antibodies may be present. Measurement of free T_4, T_3, and TSH at 2- to 4-wk intervals identifies the stages of the disease.

Prognosis

Subacute thyroiditis is self-limited, generally subsiding in a few months; occasionally, it recurs and may result in permanent hypothyroidism when follicular destruction is extensive.

Treatment

• NSAIDs

• Sometimes corticosteroids, a β-blocker, or both

Discomfort is treated with high doses of aspirin or NSAIDs. In severe and protracted cases, corticosteroids (eg, prednisone 30 to 40 mg po once/day, gradually decreasing the dose over 3 to 4 wk) eradicate all symptoms within 48 h.

Bothersome hyperthyroid symptoms may be treated with a short course of a β-blocker. If hypothyroidism is pronounced or persists, thyroid hormone replacement therapy may be required, rarely permanently.

Simple Nontoxic Goiter

(Euthyroid Goiter)

Simple nontoxic goiter, which may be diffuse or nodular, is noncancerous hypertrophy of the thyroid without hyperthyroidism, hypothyroidism, or inflammation. Except in severe iodine deficiency, thyroid function is normal and patients are asymptomatic except for an obviously enlarged, nontender thyroid. Diagnosis is clinical and with determination of normal thyroid function. Treatment is directed at the underlying cause, but partial surgical removal may be

required for very large goiters.

Simple nontoxic goiter, the most common type of thyroid enlargement, is frequently noted at puberty, during pregnancy, and at menopause. The cause at these times is usually unclear. Known causes include intrinsic thyroid hormone production defects and, in iodine-deficient countries, ingestion of foods that contain substances that inhibit thyroid hormone synthesis (goitrogens, eg, cassava, broccoli, cauliflower, cabbage). Other causes include the use of drugs that can decrease the synthesis of thyroid hormone (eg, amiodarone or other iodine-containing compounds, lithium).

Iodine deficiency is rare in North America but remains the most common cause of goiter worldwide (termed endemic goiter). Compensatory small elevations in thyroid-stimulating hormone (TSH) occur, preventing hypothyroidism, but the TSH stimulation results in goiter formation. Recurrent cycles of stimulation and involution may result in nontoxic nodular goiters. However, the true etiology of most nontoxic goiters in iodine-sufficient areas is unknown.

Symptoms and Signs

The patient may have a history of low iodine intake or overingestion of food goitrogens, but these phenomena are rare in North America. In the early stages, the goiter is typically soft, symmetric, and smooth. Later, multiple nodules and cysts may develop.

Diagnosis

• Thyroidal radioactive iodine uptake

• Thyroid scan

• Thyroxine (T_4), triiodothyronine (T_3), and TSH levels

In the early stages, thyroidal radioactive iodine uptake may be normal or high with normal thyroid scans. Thyroid function tests are usually normal. Thyroid antibodies are measured to rule out Hashimoto's thyroiditis.

In endemic goiter, serum TSH may be slightly elevated, and serum T_4 may be low-normal or slightly low, but serum T_3 is usually normal or slightly elevated.

Treatment

• Depends on cause

In iodine-deficient areas, iodine supplementation of salt; oral or IM administration of iodized oil yearly; and iodination of water, crops, or animal fodder eliminates iodine-deficiency goiter. Goitrogens being ingested should be stopped.

In other instances, suppression of the hypothalamic-pituitary axis with thyroid hormone blocks TSH production (and hence stimulation of the thyroid). Full TSH-suppressive doses of L-thyroxine (100 to 150 µg/day po depending on the serum TSH) are useful in younger patients. L-Thyroxine is contraindicated in older patients with nontoxic nodular goiter, because these goiters rarely shrink and may harbor areas of autonomy so that L-thyroxine therapy can result in hyperthyroidism. Large goiters occasionally require surgery or ^{131}I to shrink the gland enough to prevent interference with respiration or swallowing or to correct cosmetic problems.

Thyroid Cancers

The 4 general types of thyroid cancer are papillary, follicular, medullary, and anaplastic. Papillary and follicular carcinoma together are called differentiated thyroid cancer because of their histologic resemblance to normal thyroid tissue and because differentiated function (eg,

thyroglobulin secretion) is preserved. Most thyroid cancers manifest as asymptomatic nodules. Rarely, lymph node, lung, or bone metastases cause the presenting symptoms of small thyroid cancers. Diagnosis is often by fine-needle aspiration biopsy but may involve other tests. Except for anaplastic and metastatic medullary carcinoma, most thyroid cancers are not highly malignant and are seldom fatal. Treatment is surgical removal, usually followed by ablation of residual tissue with radioactive iodine.

Papillary Carcinoma

Papillary carcinoma accounts for 70 to 80% of all thyroid cancers. The female:male ratio is 3:1. It may be familial in up to 5% of patients. Most patients present between ages 30 and 60. The tumor is often more aggressive in elderly patients. Many papillary carcinomas contain follicular elements.

The tumor spreads via lymphatics to regional lymph nodes in one third of patients and may metastasize to the lungs. Patients < 45 yr with small tumors confined to the thyroid have an excellent prognosis.

Treatment

• Surgical resection

• Sometimes radioactive iodine

Treatment for encapsulated tumors < 1.5 cm localized to one lobe is usually near-total thyroidectomy, although some experts recommend only lobectomy and isthmectomy; surgery is almost always curative. Thyroid hormone in thyroid-stimulating hormone (TSH)-suppressive doses is given to minimize chances of regrowth and cause regression of any microscopic remnants of papillary carcinoma.

Tumors > 4 cm or that are diffusely spreading require total or near-total thyroidectomy with postoperative radioiodine ablation of residual thyroid tissue with appropriately large doses of ^{131}I administered when the patient is hypothyroid or after recombinant TSH injections. Treatment may be repeated every 6 to 12 mo to ablate any remaining thyroid tissue. TSH-suppressive doses of L-thyroxine are given after treatment, and serum thyroglobulin levels help detect recurrent or persistent disease. About 20 to 30% of patients, mainly older patients, have recurrent or persistent disease.

Follicular Carcinoma

Follicular carcinoma, including the Hurthle cell variant, accounts for about 15% of thyroid cancers. It is more common among older patients and in regions of iodine deficiency. It is more malignant than papillary carcinoma, spreading hematogenously with distant metastases.

Treatment requires near-total thyroidectomy with postoperative radioiodine ablation of residual thyroid tissue as in treatment for papillary carcinoma. Metastases are more responsive to radioiodine therapy than are those of papillary carcinoma. TSH-suppressive doses of L-thyroxine are given after treatment. Serum thyroglobulin should be monitored to detect recurrent or persistent disease.

Medullary Carcinoma

Medullary (solid) carcinoma constitutes about 3% of thyroid cancers and is composed of parafollicular cells (C cells) that produce calcitonin. It may be sporadic (usually unilateral); however, it is often familial, caused by a mutation of the *ret* proto-oncogene. The familial form may occur in isolation or as a component of multiple endocrine neoplasia (MEN) syndromes types 2A and 2B (see pp. 912 and 913). Although calcitonin can lower serum Ca and phosphate, serum Ca is normal because the high level of calcitonin ultimately down-regulates its receptors. Characteristic amyloid deposits that stain with Congo red are also present.

Metastases spread via the lymphatic system to cervical and mediastinal nodes and sometimes to liver, lungs, and bone.

Symptoms and Signs

Patients typically present with an asymptomatic thyroid nodule, although many cases are now diagnosed during routine screening of affected kindreds with MEN-2A or MEN-2B before a palpable tumor develops.

Medullary carcinoma may have a dramatic biochemical presentation when associated with ectopic production of other hormones or peptides (eg, ACTH, vasoactive intestinal polypeptide, prostaglandins, kallikreins, serotonin).

Diagnosis

• Serum calcitonin levels

The best test is measurement of serum calcitonin, which is greatly elevated. A challenge with Ca (15 mg/kg IV over 4 h) provokes excessive secretion of calcitonin. X-rays may show a dense, homogenous, conglomerate calcification.

All patients with medullary carcinoma should have genetic testing; relatives of those with mutations should have genetic testing and measurement of basal and stimulated calcitonin levels.

Treatment

• Surgical resection

Total thyroidectomy is indicated even if bilateral involvement is not obvious. Lymph nodes are also dissected. If hyperparathyroidism is present, removal of hyperplastic or adenomatous parathyroids is required. Pheochromocytoma, if present, is usually bilateral. Pheochromocytomas should be identified and removed before thyroidectomy because of the danger of provoking hypertensive crisis during the operation. Long-term survival is common in patients with medullary carcinoma and MEN-IIA; more than two thirds of affected patients are alive at 10 yr. Medullary carcinoma of the sporadic type has a worse prognosis.

Relatives with an elevated calcitonin level without a palpable thyroid abnormality should undergo thyroidectomy, because there is a greater chance of cure at this stage. Some experts recommend surgery in relatives who have normal basal and stimulated serum calcitonin levels but who have the *ret* proto-oncogene mutation.

Anaplastic Carcinoma

Anaplastic carcinoma is an undifferentiated cancer that accounts for about 2% of thyroid cancers. It occurs mostly in elderly patients and slightly more often in women. The tumor is characterized by rapid, painful enlargement. Rapid enlargement of the thyroid may also suggest thyroid lymphoma, particularly if found in association with Hashimoto's thyroiditis.

No effective therapy exists, and the disease is generally fatal. About 80% of patients die within 1 yr of diagnosis. In a few patients with smaller tumors, thyroidectomy followed by external radiation has been curative. Chemotherapy is mainly experimental.

Radiation-Induced Thyroid Cancer

Thyroid tumors develop in people exposed to large amounts of environmental thyroid radiation, as occurs from atomic bomb blasts, nuclear reactor accidents, or incidental thyroid irradiation due to radiation therapy. Tumors may be detected 10 yr after exposure, but risk remains increased for 30 to 40 yr. Such tumors are usually benign; however, about 10% are papillary thyroid carcinoma. The tumors are frequently multicentric or diffuse.

Patients who had thyroid irradiation should undergo yearly thyroid palpation, ultrasonography, and measurement of thyroid autoantibodies (to exclude Hashimoto's thyroiditis). A thyroid scan does not

always reflect areas of involvement.

If ultrasonography reveals a nodule, fine-needle aspiration biopsy should be done. In the absence of suspicious or malignant lesions, many physicians recommend lifelong TSH-lowering doses of thyroid hormone to suppress thyroid function and thyrotropin secretion and possibly decrease the chance of developing a thyroid tumor.

Surgery is required if fine-needle aspiration biopsy suggests cancer. Near-total or total thyroidectomy is the treatment of choice, to be followed by radioiodine ablation of any residual thyroid tissue if a cancer is found (depending on the size, histology, and invasiveness).

Chapter 94. Adrenal Disorders

Introduction

The adrenal glands, located on the cephalad portion of each kidney, consist of a cortex and medulla, each with separate endocrine functions.

Cortex: The adrenal cortex produces glucocorticoids (primarily cortisol), mineralocorticoids (primarily aldosterone), and androgens (primarily dehydroepiandrosterone and androstenedione). Physiology of the hypothalamic-pituitary-adrenocortical system is further discussed in Ch. 91.

Glucocorticoids promote and inhibit gene transcription in many cells and organ systems. Prominent effects include anti-inflammatory actions and increased hepatic gluconeogenesis.

Mineralocorticoids regulate electrolyte transport across epithelial surfaces, particularly renal conservation of Na in exchange for K.

Adrenal androgens' chief physiologic activity occurs after conversion to testosterone and dihydrotestosterone.

Medulla: The adrenal medulla is composed of chromaffin cells, which synthesize and secrete catecholamines (mainly epinephrine and lesser amounts of norepinephrine). Chromaffin cells also produce bioactive amines and peptides (eg, histamine, serotonin, chromogranins, neuropeptide hormones). Epinephrine and norepinephrine, the major effector amines of the sympathetic nervous system, are responsible for the "flight or fight" response (ie, chronotropic and inotropic effects on the heart; bronchodilation; peripheral and splanchnic vasoconstriction with skeletal muscular vasodilation; metabolic effects including glycogenolysis, lipolysis, and renin release).

Clinical syndromes: Most deficiency syndromes affect output of all adrenocortical hormones. Hypofunction may be primary (malfunction of the adrenal gland itself, as in Addison's disease) or secondary (due to lack of adrenal stimulation by the pituitary or hypothalamus, although some experts refer to hypothalamic malfunction as tertiary).

Hyperfunction causes distinct clinical syndromes. Hypersecretion of androgens results in adrenal virilism; of glucocorticoids, Cushing's syndrome; and of aldosterone, hyperaldosteronism (aldosteronism). These syndromes frequently have overlapping features. Hyperfunction may be compensatory, as in congenital adrenal hyperplasia (see p. 2889), or due to acquired hyperplasia, adenomas, or adenocarcinomas. Excess quantities of epinephrine and norepinephrine are produced in pheochromocytoma.

Addison's Disease

(Primary or Chronic Adrenocortical Insufficiency)

Addison's disease is an insidious, usually progressive hypofunctioning of the adrenal cortex. It causes various symptoms, including hypotension and hyperpigmentation, and can lead to adrenal crisis with cardiovascular collapse. Diagnosis is clinical and by finding elevated plasma ACTH with low plasma cortisol. Treatment depends on the cause but generally includes hydrocortisone and sometimes other hormones.

Addison's disease develops in about 4/100,000 annually. It occurs in all age groups, about equally in each sex, and tends to become clinically apparent during metabolic stress or trauma. Onset of severe symptoms (adrenal crisis) may be precipitated by acute infection (a common cause, especially with septicemia). Other causes include trauma, surgery, and Na loss from excessive sweating. With treatment, Addison's disease should not typically reduce life expectancy.

Etiology

About 70% of cases in the US are due to idiopathic atrophy of the adrenal cortex, probably caused by

autoimmune processes. The remainder result from destruction of the adrenal gland by granuloma (eg, TB), tumor, amyloidosis, hemorrhage, or inflammatory necrosis. Hypoadrenocorticism can also result from administration of drugs that block corticosteroid synthesis (eg, ketoconazole, the anesthetic etomidate). Addison's disease may coexist with diabetes mellitus or hypothyroidism in polyglandular deficiency syndrome (see p. 804). In children, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia (CAH—see also Congenital Adrenal Hyperplasia on p. 2889).

Pathophysiology

Both mineralocorticoids and glucocorticoids are deficient.

Mineralocorticoid deficiency: Because mineralocorticoids stimulate Na reabsorption and K excretion, deficiency results in increased excretion of Na and decreased excretion of K, chiefly in urine but also in sweat, saliva, and the GI tract. A low serum concentration of Na and a high concentration of K result. Inability to concentrate the urine, combined with changes in electrolyte balance, cause severe dehydration, plasma hypertonicity, acidosis, decreased circulatory volume, hypotension, and, eventually, circulatory collapse. However, when adrenal insufficiency is caused by inadequate ACTH production (secondary adrenal insufficiency—see p. 795), electrolyte levels are often normal or only mildly deranged.

Glucocorticoid deficiency: Glucocorticoid deficiency contributes to hypotension and causes severe insulin sensitivity and disturbances in carbohydrate, fat, and protein metabolism. In the absence of cortisol, insufficient carbohydrate is formed from protein; hypoglycemia and diminished liver glycogen result. Weakness follows, due in part to deficient neuromuscular function. Resistance to infection, trauma, and other stress is diminished. Myocardial weakness and dehydration reduce cardiac output, and circulatory failure can occur. Decreased blood cortisol results in increased pituitary ACTH production and increased blood β-lipotropin, which has melanocyte-stimulating activity and, together with ACTH, causes the hyperpigmentation of skin and mucous membranes characteristic of Addison's disease. Thus, adrenal insufficiency secondary to pituitary failure (see p. 795) does not cause hyperpigmentation.

Symptoms and Signs

Weakness, fatigue, and orthostatic hypotension are early symptoms and signs. Hyperpigmentation is characterized by diffuse tanning of exposed and, to a lesser extent, unexposed portions of the body, especially on pressure points (bony prominences), skin folds, scars, and extensor surfaces. Black freckles are common on the forehead, face, neck, and shoulders. Areas of vitiligo develop, as do bluish black discolorations of the areolae and mucous membranes of the lips, mouth, rectum, and vagina. Anorexia, nausea, vomiting, and diarrhea often occur. Decreased tolerance to cold, with hypometabolism, may be noted. Dizziness and syncope may occur. The gradual onset and nonspecific nature of early symptoms often lead to an incorrect initial diagnosis of neurosis. Weight loss, dehydration, and hypotension are characteristic of the later stages of Addison's disease.

Adrenal crisis: Adrenal crisis is characterized by profound asthenia; severe pain in the abdomen, lower back, or legs; peripheral vascular collapse; and, finally, renal shutdown with azotemia. Body temperature may be low, although severe fever often occurs, particularly when crisis is precipitated by acute infection. A significant number of patients with partial loss of adrenal function (limited adrenocortical reserve) appear well but experience adrenal crisis when under physiologic stress (eg, surgery, infection, burns, critical illness). Shock and fever may be the only signs.

Diagnosis

- Electrolytes
- Serum cortisol
- Serum ACTH
- Sometimes ACTH stimulation testing

Clinical symptoms and signs suggest adrenal insufficiency. Sometimes the diagnosis is considered only on discovery of characteristic abnormalities of serum electrolytes, including low Na (< 135 mEq/L), high K (> 5 mEq/L), low HCO_3 (15 to 20 mEq/L), and high BUN (see Table 94-1).

Differential diagnosis: Hyperpigmentation can result from bronchogenic carcinoma, ingestion of heavy metals (eg, iron, silver), chronic skin conditions, or hemochromatosis. Peutz-Jeghers syndrome is characterized by pigmentation of the buccal and rectal mucosa. Frequently, hyperpigmentation occurs with vitiligo, which may indicate Addison's disease, although other diseases can cause this association.

Weakness resulting from Addison's disease subsides with rest, unlike neuropsychiatric weakness, which is often worse in the morning than after activity. Most myopathies that cause weakness can be differentiated by their distribution, lack of abnormal pigmentation, and characteristic laboratory findings.

[**Table 94-1.** Test Results that Suggest Addison's Disease]

Patients with adrenal insufficiency develop hypoglycemia after fasting because of decreased gluconeogenesis. In contrast, patients with hypoglycemia due to oversecretion of insulin can have attacks at any time, usually have increased appetite with weight gain, and have normal adrenal function. Low serum Na due to Addison's disease must be differentiated from that of edematous patients with cardiac or liver disease (particularly those taking diuretics), the dilutional hyponatremia of the syndrome of inappropriate ADH secretion, and salt-losing nephritis. These patients are not likely to have hyperpigmentation, hyperkalemia, and increased BUN.

Testing: Laboratory tests, beginning with serum cortisol and ACTH levels, confirm adrenal insufficiency. Elevated ACTH (≥ 50 pg/mL) with low cortisol (< 5 µg/dL [< 138 nmol/L]) is diagnostic, particularly in patients who are severely stressed or in shock. Low ACTH (< 5 pg/mL) and cortisol suggest secondary adrenal insufficiency (see p. 795); it is important to note that ACTH levels within the normal range are inappropriate for very low cortisol levels.

If ACTH and cortisol levels are borderline and adrenal insufficiency is clinically suspected—particularly in a patient who is about to undergo major surgery—provocative testing must be done. If time is too short (eg, emergency surgery), the patient is given hydrocortisone empirically (eg, 100 mg IV or IM), and provocative testing is done subsequently.

Addison's disease is diagnosed by showing failure of exogenous ACTH to increase serum cortisol. Secondary adrenal insufficiency is diagnosed by a prolonged ACTH stimulation test, insulin tolerance test, or glucagon test.

ACTH stimulation testing is done by injecting cosyntropin (synthetic ACTH) 250 µg IV or IM. Some authorities believe that in patients with suspected secondary adrenal insufficiency, a low-dose ACTH stimulation test using 1 µg IV instead of the standard 250 µg should be done, because such patients may react normally to the higher dose. Patients taking glucocorticoid supplements or spironolactone should not take them on the day of the test. Normal preinjection serum cortisol ranges from 5 to 25 µg/dL (138 to 690 nmol/L) and doubles in 30 to 90 min, reaching at least 20 µg/dL (552 nmol/L). Patients with Addison's disease have low or low-normal values that do not rise above 20 µg/dL at 30 min. A normal response to cosyntropin may occur in secondary adrenal insufficiency. However, because pituitary failure may cause adrenal atrophy (and hence failure to respond to ACTH), the patient may need to be primed with long-acting ACTH 1 mg IM once/day for 3 days before the cosyntropin test if pituitary disease is suspected.

A prolonged ACTH stimulation test (sampling for 24 h) may be used to diagnose secondary (or tertiary—hypothalamic) adrenal insufficiency. Cosyntropin 1 mg IM is given and cortisol measured at intervals for 24 h. Results for the first hour are similar for both the short (sampling stopped after 1 h) and prolonged tests, but in Addison's disease there is no further rise beyond 60 min. In secondary and tertiary adrenal insufficiency, cortisol levels continue to rise for ≥ 24 h. Only in cases of prolonged adrenal atrophy is adrenal priming (with long-acting ACTH) necessary. The simple short test is usually done initially, because a normal response obviates the need for further investigation.

If adrenal crisis is suspected, confirmation of Addison's disease by ACTH stimulation testing is deferred until the patient has recovered. If ACTH stimulation testing is done, elevated ACTH levels together with low cortisol levels confirm the diagnosis.

In Western societies, the cause is usually assumed to be autoimmune, unless there is evidence otherwise. Adrenal autoantibodies can be assessed. A chest x-ray should be done for TB; if doubt exists, CT of the adrenals is helpful. In patients with autoimmune disease, the adrenals are atrophied, whereas in patients with TB or other granulomas, the adrenals are enlarged (initially) with frequent calcification. Bilateral adrenal hyperplasia suggests an enzyme defect.

Treatment

• Hydrocortisone or prednisone

• Fludrocortisone

• Dose increase during intercurrent illness

Normally, cortisol is secreted maximally in the early morning and minimally at night. Thus, hydrocortisone (identical to cortisol) is given in 2 or 3 divided doses with a typical total daily dose of 15 to 30 mg. One regimen gives half the total in the morning, and the remaining half split between lunchtime and early evening (eg, 10 mg, 5 mg, 5 mg). Others give two thirds in the morning and one third in the evening. Doses immediately before retiring should generally be avoided because they may cause insomnia. Alternatively, prednisone 5 mg po in the morning and 2.5 mg po in the evening may be used. Additionally, fludrocortisone 0.1 to 0.2 mg po once/day is recommended to replace aldosterone. The easiest way to adjust the dosage is to ensure that the renin level is within the normal range. Normal hydration and absence of orthostatic hypotension are evidence of adequate replacement therapy. In some patients, fludrocortisone causes hypertension, which is treated by reducing the dosage or starting a nondiuretic antihypertensive. Some clinicians tend to give too little fludrocortisone in an effort to avoid use of antihypertensives.

Intercurrent illnesses (eg, infections) are potentially serious and should be vigorously treated; the patient's hydrocortisone dose should be doubled during the illness. If nausea and vomiting preclude oral therapy, parenteral therapy is necessary. Patients should be instructed when to take supplemental prednisone and taught to self-administer parenteral hydrocortisone for urgent situations. A preloaded syringe with 100 mg hydrocortisone should be available to the patient. A bracelet or wallet card giving the diagnosis and corticosteroid dose may help in case of adrenal crisis that renders the patient unable to communicate. When salt loss is severe, as in very hot climates, the dose of fludrocortisone may need to be increased.

In coexisting diabetes mellitus and Addison's disease, the hydrocortisone dose usually should not be > 30 mg/day; otherwise, insulin requirements are increased.

Adrenal crisis: Therapy should be instituted immediately upon suspicion. (CAUTION: *In adrenal crisis, a delay in instituting corticosteroid therapy, particularly if there is hypoglycemia and hypotension, may be fatal.*) If the patient is acutely ill, confirmation by an ACTH stimulation test should be postponed until the patient has recovered.

Hydrocortisone 100 mg is injected IV over 30 sec and repeated q 6 to 8 h for the first 24 h. Immediate intravascular volume expansion is done by giving 1 L of a 5% dextrose in 0.9% saline solution over 1 to 2 h. Additional 0.9% saline is given IV until hypotension, dehydration, and hyponatremia have been corrected. Serum K may fall during rehydration, requiring replacement. Mineralocorticoids are not required when high-dose hydrocortisone is given. When illness is less acute, hydrocortisone 50 or 100 mg can be given IM q 6 h. Restoration of BP and general improvement should occur within 1 h after the initial dose of hydrocortisone. Inotropic agents may be needed until the effects of hydrocortisone are achieved.

A total dose of 150 mg hydrocortisone is usually given over the 2nd 24-h period if the patient has improved markedly, and 75 mg is given on the 3rd day. Maintenance oral doses of hydrocortisone (15 to

30 mg) and fludrocortisone (0.1 mg) are given daily thereafter, as described above. Recovery depends on treatment of the underlying cause (eg, infection, trauma, metabolic stress) and adequate hydrocortisone therapy.

For patients with some residual adrenal function who develop adrenal crisis when under stress, hydrocortisone treatment is the same, but fluid requirements may be much lower.

Treatment of complications: Fever > 40.6° C occasionally accompanies the rehydration process. Except in the presence of falling BP, antipyretics (eg, aspirin 650 mg) may be given po with caution. Complications of corticosteroid therapy may include psychotic reactions. If psychotic reactions occur after the first 12 h of therapy, the hydrocortisone dose should be reduced to the lowest level consistent with maintaining BP and good cardiovascular function. Antipsychotics may be temporarily required, but use should not be prolonged.

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency is adrenal hypofunction due to a lack of ACTH. Symptoms are the same as for Addison's disease, but there is usually less hypovolemia (see p. 792). Diagnosis is clinical and by laboratory findings, including low plasma ACTH with low plasma cortisol. Treatment depends on the cause but generally includes hydrocortisone.

Secondary adrenal insufficiency may occur in panhypopituitarism, in isolated failure of ACTH production, in patients receiving corticosteroids, or after corticosteroids are stopped. Inadequate ACTH can also result from failure of the hypothalamus to stimulate pituitary ACTH production, which is sometimes called tertiary adrenal insufficiency.

Panhypopituitarism (see p. 762) may occur secondary to pituitary tumors; craniopharyngioma in younger people; and various tumors, granulomas, and, rarely, infection or trauma that destroys pituitary tissue. Patients receiving corticosteroids for > 4 wk may have insufficient ACTH secretion during metabolic stress to stimulate the adrenals to produce adequate quantities of corticosteroids, or they may have atrophic adrenals that are unresponsive to ACTH. These problems may persist for up to 1 yr after corticosteroid treatment is stopped.

Symptoms and Signs

Symptoms and signs are similar to those of Addison's disease (see p. 792). Differentiating clinical or general laboratory features include the absence of hyperpigmentation and relatively normal electrolyte and BUN levels; hyponatremia, if it occurs, is usually dilutional.

Patients with panhypopituitarism have depressed thyroid and gonadal function and hypoglycemia, and coma may supervene when symptomatic secondary adrenal insufficiency occurs. Adrenal crisis is especially likely if a patient is treated for a single endocrine gland problem, particularly with thyroxine, without hydrocortisone replacement.

Diagnosis

• Serum cortisol

• Serum ACTH

• ACTH stimulation testing

• CNS imaging

Tests to differentiate primary and secondary adrenal insufficiency are discussed under Addison's disease (see p. 793). Patients with confirmed secondary adrenal insufficiency should have CT or MRI of the brain to rule out pituitary tumor or atrophy. Adequacy of the hypothalamic-pituitary-adrenal axis during tapering or after stopping long-term corticosteroid treatment can be determined by injecting cosyntropin 250 µg IV

or IM. After 30 min, serum cortisol should be > 20 µg/dL (> 552 nmol/L). An insulin stress test to induce hypoglycemia and a rise in cortisol is the gold standard for testing integrity of the hypothalamic-pituitary-adrenal axis.

The corticotropin-releasing hormone (CRH) test can be used to distinguish between hypothalamic and pituitary causes but is rarely used in clinical practice. After administration of CRH 100 µg (or 1 µg/kg) IV, the normal response is a rise of serum ACTH of 30 to 40 pg/mL; patients with pituitary failure do not respond, whereas those with hypothalamic disease usually do.

Treatment

• Hydrocortisone or prednisone

• Fludrocortisone not indicated

• Dose increase during intercurrent illness

Glucocorticoid replacement is similar to that described for Addison's disease. Each case varies regarding the type and degree of specific hormone deficiencies. Fludrocortisone is not required because the intact adrenals produce aldosterone. During acute febrile illness or after trauma, patients receiving corticosteroids for nonendocrine disorders may require supplemental doses to augment their endogenous hydrocortisone production. In panhypopituitarism, other pituitary deficiencies should be treated appropriately (see p. 766).

Adrenal Virilism

(Adrenogenital Syndrome)

Adrenal virilism is a syndrome in which excessive adrenal androgens cause virilization. Diagnosis is clinical and confirmed by elevated androgen levels with and without dexamethasone suppression; determining the cause may involve adrenal imaging. Treatment depends on the cause.

Adrenal virilism is caused by an androgen-secreting adrenal tumor or by adrenal hyperplasia. Malignant adrenal tumors may secrete excess androgens, cortisol, or mineralocorticoids (or all three), resulting in Cushing's syndrome (see p. 797) with suppression of ACTH secretion and atrophy of the contralateral adrenal as well as hypertension. Adrenal hyperplasia is usually congenital; delayed virilizing adrenal hyperplasia is a variant of congenital adrenal hyperplasia (see p. 2889). Both are caused by a defect in hydroxylation of cortisol precursors; cortisol precursors accumulate and are shunted into the production of androgens. The defect is only partial in delayed virilizing adrenal hyperplasia, so clinical disease may not develop until adulthood.

Symptoms and Signs

Effects depend on the patient's sex and age at onset and are more noticeable in women than in men. Symptoms and signs include hirsutism (sometimes the only sign in mild cases), baldness, acne, and deepening of the voice. Libido may increase. In prepubertal children, growth may accelerate. If untreated, premature epiphyseal closure and short stature occur. Affected prepubertal males may experience premature sexual maturation. Females may have amenorrhea, atrophy of the uterus, clitoral hypertrophy, decreased breast size, and increased muscularity. In adult men, the excess adrenal androgens may suppress gonadal function and cause infertility. Ectopic adrenal tissue in the testes may enlarge and simulate tumors.

Diagnosis

• Testosterone

• Other adrenal androgens (dehydroepiandrosterone sulfate [DHEAS], androstenedione)

• Dexamethasone suppression test

• Adrenal imaging

• 17-hydroxyprogesterone

Adrenal virilism is suspected clinically, although mild hirsutism and virilization with hypomenorrhea and elevated plasma testosterone may also occur in polycystic ovary (Stein-Leventhal) syndrome (see p. 2514). Adrenal virilism is confirmed by showing elevated levels of adrenal androgens. In adrenal hyperplasia, urinary dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are elevated, pregnanetriol excretion is often increased, and urinary free cortisol is normal or diminished. Plasma DHEA, DHEAS, 17-hydroxyprogesterone, testosterone, and androstenedione may be elevated. A level of > 30 nmol/L of 17-hydroxyprogesterone 30 min after administration of cosyntropin 0.25 mg IM strongly suggests the most common form of adrenal hyperplasia.

Virilizing tumors are excluded if dexamethasone 0.5 mg po q 6 h for 48 h suppresses production of excess androgens. If excessive androgen excretion is not suppressed, CT or MRI of the adrenals and ultrasonography of the ovaries are done to search for a tumor.

Treatment

• Oral corticosteroids for hyperplasia

• Removal of tumors

Recommended treatment for adrenal hyperplasia is dexamethasone 0.5 to 1 mg po at bedtime, but even these small doses may cause signs of Cushing's syndrome. Cortisol 25 mg po once/day or prednisone 5 to 10 mg po once/day can be used instead. Although most symptoms and signs of virilism disappear, hirsutism and baldness disappear slowly, the voice may remain deep, and fertility may be impaired.

Tumors require adrenalectomy. For patients with cortisol-secreting tumors, hydrocortisone should be given preoperatively and postoperatively because their nontumerous adrenal cortex will be atrophic and suppressed.

Cushing's Syndrome

Cushing's syndrome is a constellation of clinical abnormalities caused by chronic high blood levels of cortisol or related corticosteroids. Cushing's disease is Cushing's syndrome that results from excess pituitary production of ACTH, usually secondary to a pituitary adenoma. Typical symptoms include moon facies and truncal obesity with thin arms and legs. Diagnosis is by history of receiving corticosteroids or by finding elevated serum cortisol. Treatment depends on the cause.

Etiology

Hyperfunction of the adrenal cortex can be ACTH dependent or ACTH independent. ACTH-dependent hyperfunction may result from

• Hypersecretion of ACTH by the pituitary gland

• Secretion of ACTH by a nonpituitary tumor, such as small cell carcinoma of the lung or a carcinoid tumor (ectopic ACTH syndrome)

• Administration of exogenous ACTH

ACTH-independent hyperfunction usually results from therapeutic administration of corticosteroids or from adrenal adenomas or carcinomas. Rare causes include primary pigmented nodular adrenal dysplasia

(usually in adolescents) and macronodular dysplasia (in older patients).

Whereas the term Cushing's syndrome denotes the clinical picture resulting from cortisol excess from any cause, Cushing's disease refers to hyperfunction of the adrenal cortex from pituitary ACTH excess. Patients with Cushing's disease usually have a small adenoma of the pituitary gland.

Symptoms and Signs

Clinical manifestations include moon facies with a plethoric appearance (see Plate 22), truncal obesity with prominent supraclavicular and dorsal cervical fat pads (buffalo hump), and, usually, very slender distal extremities and fingers. Muscle wasting and weakness are present. The skin is thin and atrophic, with poor wound healing and easy bruising. Purple striae may appear on the abdomen. Hypertension, renal calculi, osteoporosis, glucose intolerance, reduced resistance to infection, and mental disturbances are common. Cessation of linear growth is characteristic in children. Females usually have menstrual irregularities. In females with adrenal tumors, increased production of androgens may lead to hypertrichosis, temporal balding, and other signs of virilism.

Diagnosis

• Dexamethasone suppression test

• Urinary free cortisol (UFC) level

• ACTH levels; if detectable, provocative testing

Diagnosis is usually suspected based on the characteristic symptoms and signs. Confirmation (and identification of the cause) generally requires hormonal and imaging tests.

In some centers, testing begins with measurement of UFC, the best assay for urinary excretion (normal, 20 to 100 µg/24 h [55.2 to 276 nmol/24 h]). UFC is elevated > 120 µg/24 h (> 331 nmol/24 h) in almost all patients with Cushing's syndrome. However, many patients with UFC elevations between 100 and 150 µg/24 h (276 and 414 nmol/24 h) have obesity, depression, or polycystic ovaries but not Cushing's syndrome. A patient with suspected Cushing's syndrome with grossly elevated UFC (> 4 times the upper limit of normal) almost certainly has Cushing's syndrome. Two to 3 normal collections virtually exclude the diagnosis. Slightly elevated levels generally necessitate further investigation.

An alternative approach to investigation uses the dexamethasone suppression test, in which 1, 1.5, or 2 mg of dexamethasone is given po at 11 to 12 PM and serum cortisol is measured at 8 to 9 AM the next morning. In most normal patients, this drug suppresses morning serum cortisol to ≤ 1.8 µg/mL (≤ 50 nmol/L), whereas patients with Cushing's syndrome virtually always have a higher level. A more specific but equally sensitive test is to give dexamethasone 0.5 mg po q 6 h for 2 days (low dose). In general, a clear failure to suppress levels in response to low-dose dexamethasone establishes the diagnosis.

If results of these tests are indeterminate, the patient is hospitalized for measurement of serum cortisol at midnight, which is more likely to be conclusive. Cortisol normally ranges from 5 to 25 µg/dL (138 to 690 nmol/L) in the early morning (6 to 8 AM) and declines gradually to < 1.8 µg/dL (< 50 nmol/L) at midnight. Patients with Cushing's syndrome occasionally have a normal morning cortisol level but lack normal diurnal decline in cortisol production, such that the midnight serum cortisol levels are above normal and the total 24-h cortisol production is elevated. Alternatively, salivary cortisol samples may be collected and stored in the refrigerator at home. Serum cortisol may be spuriously elevated in patients with congenital increases of corticosteroid-binding globulin or in those receiving estrogen therapy, but diurnal variation is normal in these patients.

ACTH levels are measured to determine the cause of Cushing's syndrome. Undetectable levels, both basally and particularly in response to corticotropin-releasing hormone (CRH), suggest a primary adrenal cause. High levels suggest a pituitary cause. If ACTH is detectable (ACTH-dependent Cushing's syndrome), provocative tests help differentiate Cushing's disease from ectopic ACTH syndrome, which is rarer. In response to high-dose dexamethasone (2 mg po q 6 h for 48 h), the 9 AM serum cortisol falls by

> 50% in most patients with Cushing's disease but infrequently in those with ectopic ACTH syndrome. Conversely, ACTH rises by > 50% and cortisol rises by > 20% in response to human or ovine-sequence CRH (100 µg IV or 1 µg/kg IV) in most patients with Cushing's disease but very rarely in those with ectopic ACTH syndrome (see Table 94-2). An alternative approach to localization, which is more accurate but more invasive, is to catheterize both petrosal veins (which drain the pituitary) and measure ACTH from these veins 5 min after a bolus of CRH 100 µg or 1 µg/kg. A central-to-peripheral ACTH ratio > 3 virtually excludes ectopic ACTH syndrome, whereas a ratio < 3 suggests a need to seek such a source.

Pituitary imaging is done if ACTH levels and provocative tests suggest a pituitary cause; gadolinium-enhanced MRI is most accurate, but some microadenomas are visible on CT. If testing suggests a nonpituitary cause, imaging includes high-resolution CT of the chest, pancreas, and adrenals; scintiscanning with radiolabeled octreotide; and PET scanning.

In children with Cushing's disease, pituitary tumors are very small and usually cannot be detected with MRI. Petrosal sinus sampling is particularly useful in this situation. MRI is preferred to CT in pregnant women to avoid fetal exposure to radiation.

Treatment

• Metyrapone or ketoconazole

• Surgery or radiation to remove tumors

[**Table 94-2.** Diagnostic Tests in Cushing's Syndrome]

Initially, the patient's general condition should be supported by high protein intake and appropriate administration of K. If clinical manifestations are severe, it may be reasonable to block corticosteroid secretion with metyrapone 250 mg to 1 g po tid or ketoconazole 400 mg po once/day, increasing to a maximum of 400 mg tid. Ketoconazole is more readily available but slower in onset and sometimes hepatotoxic.

Pituitary tumors that produce excessive ACTH are removed surgically or extirpated with radiation. If no tumor is shown on imaging but a pituitary source is likely, total hypophysectomy may be attempted, particularly in older patients. Younger patients usually receive supervoltage irradiation of the pituitary, delivering 45 Gy. Improvement usually occurs in < 1 yr. However, in children, irradiation may reduce secretion of growth hormone and occasionally cause precocious puberty. In special centers, heavy particle beam irradiation, providing about 100 Gy, is often successful, as is a single focused beam of radiation therapy given as a single dose—radiosurgery. Response to irradiation occasionally requires several years, but response is more rapid in children.

Bilateral adrenalectomy is reserved for patients with pituitary hyperadrenocorticism who do not respond to both pituitary exploration (with possible adenomectomy) and irradiation. Adrenalectomy requires life-long corticosteroid replacement.

Nelson syndrome occurs when the pituitary gland continues to expand after adrenalectomy, causing a marked increase in the secretion of ACTH and its precursors, resulting in severe hyperpigmentation. It occurs in ≤ 50% of patients who undergo adrenalectomy. The risk is probably reduced if the patient undergoes pituitary radiation. Although irradiation may arrest continued pituitary growth, many patients also require hypophysectomy. The indications for hypophysectomy are the same as for any pituitary tumor: an increase in size such that the tumor encroaches on surrounding structures, causing visual field defects, pressure on the hypothalamus, or other complications. Routine irradiation is often done after hypophysectomy if it was not done previously, especially when a tumor is clearly present. Radiosurgery, or focused radiation therapy, can be given in a single fraction when standard external beam radiation therapy has already been done, as long as the lesion is at a reasonable distance from the optic nerve and chiasm.

Adrenocortical tumors are removed surgically. Patients must receive cortisol during the surgical and

postoperative periods because their nontumorous adrenal cortex will be atrophic and suppressed. Benign adenomas can be removed laparoscopically. With multinodular adrenal hyperplasia, bilateral adrenalectomy may be necessary. Even after a presumed total adrenalectomy, functional regrowth occurs in a few patients.

Ectopic ACTH syndrome is treated by removing the nonpituitary tumor that is producing the ACTH. However, in some cases, the tumor is disseminated and cannot be excised. Adrenal inhibitors, such as metyrapone 500 mg po tid (and up to a total of 6 g/day) or mitotane 0.5 g po once/day, increasing to a maximum of 3 to 4 g/day, usually control severe metabolic disturbances (eg, hypokalemia). When mitotane is used, large doses of hydrocortisone or dexamethasone may be needed. Measures of cortisol production may be unreliable, and severe hypercholesterolemia may develop. Ketoconazole 400 to 1200 mg po once/day also blocks corticosteroid synthesis, although it may cause liver toxicity and can cause addisonian symptoms. Alternatively, the corticosteroid receptors can be blocked with mifepristone (RU 486). Mifepristone increases serum cortisol but blocks effects of the corticosteroid. Sometimes ACTH-secreting tumors respond to long-acting somatostatin analogs, although administration for > 2 yr requires close follow-up, because mild gastritis, gallstones, cholangitis, and malabsorption may develop.

Primary Aldosteronism

(Conn's Syndrome)

Primary aldosteronism is aldosteronism caused by autonomous production of aldosterone by the adrenal cortex (due to hyperplasia, adenoma, or carcinoma). Symptoms and signs include episodic weakness, elevated BP, and hypokalemia. Diagnosis includes measurement of plasma aldosterone levels and plasma renin activity. Treatment depends on cause. A tumor is removed if possible; in hyperplasia, spironolactone or related drugs may normalize BP and eliminate other clinical features.

Aldosterone is the most potent mineralocorticoid produced by the adrenals. It causes Na retention and K loss. In the kidney, aldosterone causes transfer of Na from the lumen of the distal tubule into the tubular cells in exchange for K and hydrogen. The same effect occurs in salivary glands, sweat glands, cells of the intestinal mucosa, and in exchanges between ICFs and ECFs.

Aldosterone secretion is regulated by the renin-angiotensin system and, to a lesser extent, by ACTH. Renin, a proteolytic enzyme, is stored in the juxtaglomerular cells of the kidneys. Reduction in blood volume and flow in the afferent renal arterioles induces secretion of renin. Renin transforms angiotensinogen from the liver to angiotensin I, which is transformed by ACE to angiotensin II. Angiotensin II causes secretion of aldosterone and, to a much lesser extent, secretion of cortisol and deoxycorticosterone; it also has pressor activity. Na and water retention resulting from increased aldosterone secretion increases the blood volume and reduces renin secretion.

Primary aldosteronism is caused by an adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex or, more rarely, by adrenal carcinoma or hyperplasia. Adenomas are extremely rare in children, but the syndrome sometimes occurs in childhood adrenal carcinoma or hyperplasia. In adrenal hyperplasia, which is more common among older men, both adrenals are overactive, and no adenoma is present. The clinical picture can also occur with congenital adrenal hyperplasia from deficiency of 11 β-hydroxylase and the dominantly inherited dexamethasone-suppressible hyperaldosteronism. Hyperplasia as a cause of hyperaldosteronism may be more common than previously recognized but remains an infrequent cause in the presence of hypokalemia.

Symptoms and Signs

Hypernatremia, hypervolemia, and a hypokalemic alkalosis may occur, causing episodic weakness, paresthesias, transient paralysis, and tetany. Diastolic hypertension and hypokalemic nephropathy with polyuria and polydipsia are common. In many cases, the only manifestation is mild to moderate hypertension. Edema is uncommon.

Diagnosis

• Electrolytes

• Plasma aldosterone

• Plasma renin activity (PRA)

• Adrenal imaging

• Bilateral adrenal vein catheterization (for cortisol and aldosterone levels)

Diagnosis is suspected in patients with hypertension and hypokalemia. Initial laboratory testing consists of plasma aldosterone levels and PRA. Ideally, tests are done after the patient has not taken any drugs that affect the renin-angiotensin system (eg, thiazide diuretics, ACE inhibitors, angiotensin antagonists, β-blockers) for 4 to 6 wk. PRA is usually measured in the morning with the patient recumbent. Patients with primary aldosteronism typically have plasma aldosterone > 15 ng/dL (> 0.42 nmol/L) and low levels of PRA, with a ratio of plasma aldosterone (in ng/dL) to PRA (in ng/mL/h) > 20.

Low levels of both PRA and aldosterone suggest nonaldosterone mineralocorticoid excess (eg, due to licorice ingestion, Cushing's syndrome, or Liddle syndrome). High levels of both PRA and aldosterone suggest secondary hyperaldosteronism (see p. 801). The principal differences between primary and secondary aldosteronism are shown in
Table 94-3. In children, Bartter syndrome

[**Table 94-3.** Differential Diagnosis of Aldosteronism]

(see p. 2988) is distinguished from primary hyperaldosteronism by the absence of hypertension and marked elevation of renin.

Patients with findings suggesting primary hyperaldosteronism should undergo CT or MRI to determine whether the cause is a tumor or hyperplasia. Aldosterone levels measured on awakening and 2 to 4 h later while standing also may help make this distinction; in adenoma, levels decline and in hyperplasia, levels increase. In most cases, bilateral catheterization of the adrenal veins to measure cortisol and aldosterone should be used to confirm whether the aldosterone excess is unilateral (tumor) or bilateral (hyperplasia).

Treatment

• Surgical removal of tumors

• Spironolactone or eplerenone for hyperplasia

Tumors should be removed laparoscopically. After removal of an adenoma, BP decreases in all patients; complete remission occurs in 50 to 70%.

With adrenal hyperplasia, 70% remain hypertensive after bilateral adrenalectomy; thus, surgery is not recommended. Hyperaldosteronism in these patients can usually be controlled by spironolactone, starting with 300 mg po once/day and decreasing over 1 mo to a maintenance dose, usually around 100 mg once/day; or by amiloride 5 to 10 mg po once/day or another K-sparing diuretic. The newer more specific drug eplerenone may be used because, unlike spironolactone, it does not block the androgen receptor. About half of patients with hyperplasia need additional antihypertensive treatment (see p. 2069).

Secondary Aldosteronism

Secondary aldosteronism is increased adrenal production of aldosterone in response to nonpituitary, extra-adrenal stimuli, including renal artery stenosis and hypovolemia. Symptoms are those of primary aldosteronism. Treatment involves correcting the cause.

Secondary aldosteronism is caused by reduced renal blood flow, which stimulates the renin-angiotensin mechanism with resultant hypersecretion of aldosterone. Causes of reduced renal blood flow include obstructive renal artery disease (eg, atheroma, stenosis), renal vasoconstriction (as occurs in accelerated hypertension), and edematous disorders (eg, heart failure, cirrhosis with ascites, nephrotic syndrome). Secretion may be normal in heart failure, but hepatic blood flow and aldosterone metabolism are reduced, so circulating levels of the hormone are high.

Pheochromocytoma

A pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells typically located in the adrenals. It causes persistent or paroxysmal hypertension. Diagnosis is by measuring catecholamine products in blood or urine. Imaging tests, especially CT or MRI, help localize tumors. Treatment involves removal of the tumor when possible. Drug therapy for control of BP includes α-blockade, usually combined with β-blockade.

The catecholamines secreted include norepinephrine, epinephrine, dopamine, and dopa in varying proportions. About 90% of pheochromocytomas are in the adrenal medulla, but they may also be located in other tissues derived from neural crest cells. Possible sites include the following:

• Paraganglia of the sympathetic chain

• Retroperitoneally along the course of the aorta

• Carotid body

• Organ of Zuckerkandl (at the aortic bifurcation)

• GU system

• Brain

• Pericardial sac

• Dermoid cysts

Pheochromocytomas in the adrenal medulla occur equally in both sexes, are bilateral in 10% of cases (20% in children), and are malignant in < 10%. Of extra-adrenal tumors, 30% are malignant. Although pheochromocytomas occur at any age, peak incidence is between the 20s and 40s. About 25% are now thought to be due to germline mutations.

Pheochromocytomas vary in size but average 5 to 6 cm in diameter. They weigh 50 to 200 g, but tumors weighing several kilograms have been reported. Rarely, they are large enough to be palpated or cause symptoms due to pressure or obstruction. Regardless of the histologic appearance, the tumor is considered benign if it has not invaded the capsule and no metastases are found, although exceptions occur.

Pheochromocytomas may be part of the syndrome of familial multiple endocrine neoplasia (MEN), types 2A and 2B, in which other endocrine tumors (parathyroid or medullary carcinoma of the thyroid) coexist or develop subsequently (see p. 909). Pheochromocytoma develops in 1% of patients with neurofibromatosis (von Recklinghausen's disease) and may occur with hemangiomas and renal cell carcinoma, as in von Hippel-Lindau disease. Familial pheochromocytomas and carotid body tumors may be due to mutations of the enzyme succinate dehydrogenase.

Symptoms and Signs

Hypertension, which is paroxysmal in 45% of patients, is prominent. About 1/1000 hypertensive patients has a pheochromocytoma. Common symptoms and signs are tachycardia, diaphoresis, postural hypotension, tachypnea, cold and clammy skin, severe headache, angina, palpitations, nausea, vomiting,

epigastric pain, visual disturbances, dyspnea, paresthesias, constipation, and a sense of impending doom. Paroxysmal attacks may be provoked by palpation of the tumor, postural changes, abdominal compression or massage, induction of anesthesia, emotional trauma, unopposed β-blockade (which paradoxically increases BP by blocking β-mediated vasodilation), or micturition (if the tumor is in the bladder). In elderly patients, severe weight loss with persistent hypertension is suggestive of pheochromocytoma.

Physical examination, except for the presence of hypertension, is usually normal unless done during a paroxysmal attack. Retinopathy and cardiomegaly are often less severe than might be expected for the degree of hypertension, but a specific catecholamine cardiomyopathy can occur.

Diagnosis

• Plasma free metanephrines or urinary metanephrines

• Chest and abdomen imaging (CT or MRI) if catecholamine screen positive

• Possibly nuclear imaging with ^{123}I-meta-iodobenzylguanidine (MIBG)

Pheochromocytoma is suspected in patients with typical symptoms or particularly sudden, severe, or intermittent unexplained hypertension. Diagnosis involves demonstrating high levels of catecholamine products in the serum or urine.

Blood tests: Plasma free metanephrine is up to 99% sensitive. This test has superior sensitivity to measurement of circulating epinephrine and norepinephrine because plasma metanephrines are elevated continuously, unlike epinephrine and norepinephrine, which are secreted intermittently; however, grossly elevated plasma norepinephrine renders the diagnosis highly probable.

Urine tests: Urinary metanephrine is less specific than plasma free metanephrine, but sensitivity is about 95%. Two or 3 normal results while the patient is hypertensive render the diagnosis extremely unlikely. Measurement of urinary norepinephrine and epinephrine is nearly as accurate. The principal urinary metabolic products of epinephrine and norepinephrine are the metanephrines vanillylmandelic acid (VMA) and homovanillic acid (HVA). Healthy people excrete only very small amounts of these substances. Normal values for 24 h are as follows: free epinephrine and norepinephrine < 100 µg (< 582 nmol), total metanephrine < 1.3 mg (< 7.1 µmol), VMA < 10 mg (< 50 µmol), HVA < 15 mg (< 82.4 µmol). In pheochromocytoma, increased urinary excretion of epinephrine and norepinephrine and their metabolic products is intermittent. Elevated excretion of these compounds may also occur in other disorders (eg, neuroblastoma, coma, dehydration, sleep apnea) or extreme stress; in patients being treated with rauwolfia alkaloids, methyldopa, or catecholamines; or after ingestion of foods containing large quantities of vanilla (especially if renal insufficiency is present).

Other tests: Blood volume is constricted and may falsely elevate Hb and Hct levels. Hyperglycemia, glycosuria, or overt diabetes mellitus may be present, with elevated fasting levels of plasma free fatty acid and glycerol. Plasma insulin level is inappropriately low for the plasma glucose. After removal of the pheochromocytoma, hypoglycemia may occur, especially in patients treated with oral antihyperglycemics.

Provocative tests with histamine or tyramine *are hazardous and should not be used.* Glucagon 0.5 to 1 mg injected rapidly IV provokes a rise in BP of > 35/25 mm Hg within 2 min in normotensive patients with pheochromocytoma but is now generally unnecessary. *Phentolamine mesylate must be available to terminate any hypertensive crisis.*

Screening tests are preferred to provocative tests. The general approach is to measure plasma metanephrines, 24-h urinary catecholamines, or their metabolites as a screening test and to avoid provocative tests. In patients with elevated plasma catecholamines, a suppression test using oral clonidine or IV pentolinium can be used but is rarely necessary.

Imaging tests to localize tumors are usually done in patients with abnormal screening results. Tests should include CT and MRI of the chest and abdomen with and without contrast. With isotonic contrast

media, no adrenoceptor blockade is necessary. PET has also been used successfully. Repeated sampling of plasma catecholamine concentrations during catheterization of the vena cava with sampling at different locations, including the adrenal veins, can help localize the tumor: there will be a step up in norepinephrine level in a vein draining the tumor. Adrenal vein norepinephrine:epinephrine ratios may help in the hunt for a small adrenal source. Radiopharmaceuticals with nuclear imaging techniques can also help localize pheochromocytomas. ^{123}I-MIBG is the most used compound outside the US; 0.5 mCi is injected IV, and the patient is scanned on days 1, 2, and 3. Normal adrenal tissue rarely picks up this isotope, but 85% of pheochromocytomas do. The imaging is usually positive only when the lesion is large enough to be obvious on CT or MRI, but it can help confirm that a mass is likely to be the source of the catecholamines. ^{131}I-MIBG is a less sensitive alternative.

Signs of an associated genetic disorder (eg, cafe-au-lait patches in neurofibromatosis) should be sought. Patients should be screened for MEN with a serum Ca (and possibly calcitonin) and any other tests as directed by clinical findings.

Treatment

• Hypertension control with combination of α-blockers and β-blockers

• Surgical removal of tumor

Surgical removal is the treatment of choice. The operation is usually delayed until hypertension is controlled by a combination of α-blockers and β-blockers (usually phenoxybenzamine 20 to 40 mg po tid and propranolol 20 to 40 mg po tid). β-Blockers should not be used until adequate α-blockade has been achieved. Some α-blockers, such as doxazosin, may be equally effective but better tolerated.

The most effective and safest preoperative α-blockade is phenoxybenzamine 0.5 mg/kg IV in 0.9% saline over 2 h on each of the 3 days before the operation. Na nitroprusside can be infused for hypertensive crises preoperatively or intraoperatively. When bilateral tumors are documented or suspected (as in a patient with MEN), sufficient hydrocortisone (100 mg IV bid) given before and during surgery avoids acute glucocorticoid insufficiency due to bilateral adrenalectomy.

Most pheochromocytomas can be removed laparoscopically. BP must be continuously monitored via an intra-arterial catheter, and volume status is closely monitored. Anesthesia should be induced with a nonarrhythmogenic drug (eg, a thiobarbiturate) and continued with enflurane. During surgery, paroxysms of hypertension should be controlled with injections of phentolamine 1 to 5 mg IV or nitroprusside infusion (2 to 4 µg/kg/min), and tachyarrhythmias should be controlled with propranolol 0.5 to 2 mg IV. If a muscle relaxant is needed, drugs that do not release histamine are preferred. *Atropine should not be used preoperatively.* Preoperative blood transfusion (1 to 2 units) may be given before the tumor is removed in anticipation of blood loss. If BP has been well controlled before surgery, a diet high in salt is recommended to increase blood volume. An infusion of norepinephrine 4 to 12 mg/L in a dextrose-containing solution should be started if hypotension develops. Some patients whose hypotension responds poorly to levarterenol may benefit from hydrocortisone 100 mg IV, but adequate fluid replacement is usually all that is required.

Malignant metastatic pheochromocytoma should be treated with α- and β-blockers. The tumor may be indolent and survival long-lasting. However, even with rapid tumor growth, BP can be controlled. ^{131}I-MIBG prolongs life when used to treat residual disease. Radiation therapy may reduce bone pain; chemotherapy is rarely effective but can be attempted if all else fails.

Nonfunctional Adrenal Masses

Nonfunctional adrenal masses are spaceoccupying lesions of the adrenal glands that have no hormonal activity. Symptoms, signs, and treatment depend on the nature and size of the mass.

The most common nonfunctioning adrenal mass in adults is an adenoma (50%), followed by carcinomas and metastatic tumors. Cysts and lipomas make up most of the remainder. However, the precise

proportions depend on the clinical presentation. Masses discovered on incidental screening are usually adenomas. Less commonly, in neonates, spontaneous adrenal hemorrhage may cause large adrenal masses, simulating neuroblastoma or Wilms' tumor. In adults, bilateral massive adrenal hemorrhage may result from thromboembolic disease or coagulopathy. Benign cysts are observed in elderly patients and may be due to cystic degeneration, vascular accidents, lymphomas, bacterial infections, fungal infections (eg, histoplasmosis), or parasitic infestations (eg, due to *Echinococcus*). Hematogenous spread of TB organisms may cause adrenal masses. A nonfunctional adrenal carcinoma produces a diffuse and infiltrating retroperitoneal process. Hemorrhage can occur, causing adrenal hematomas.

Symptoms and Signs

Most patients are asymptomatic. With any adrenal mass, adrenal insufficiency is rare unless both glands are involved.

The major signs of bilateral massive adrenal hemorrhage are abdominal pain, falling Hct, signs of acute adrenal failure, and suprarenal masses on CT or MRI. TB of the adrenals may cause calcification and Addison's disease. Nonfunctional adrenal carcinoma usually manifests as metastatic disease and may therefore not be amenable to surgery, though mitotane may afford chemotherapeutic control when used with supportive exogenous corticosteroids.

Diagnosis

• Adrenal hormone measurements

• Fine-needle biopsy

Nonfunctional adrenal masses are usually found incidentally during tests such as CT or MRI conducted for other reasons. Nonfunctionality is established clinically and confirmed by adrenal hormonal measurements (see p. 797). If metastatic disease is possible, fine-needle biopsy can be diagnostic but is contraindicated if adrenal carcinoma is strongly suspected.

Treatment

• Excision

• Periodic monitoring

If the tumor is solid, of adrenal origin, and > 4 cm, it should be excised, because biopsy cannot always distinguish benign from malignant tumors.

Tumors 2 to 4 cm in diameter are a particularly difficult clinical problem. If scanning does not suggest cancer and hormonal function does not seem altered (eg, normal electrolytes and catecholamines, no evidence of Cushing's syndrome), it is reasonable to reevaluate periodically, usually for up to 4 yr. If no progression is seen by then, further follow-up is unnecessary. However, many of these tumors secrete cortisol in quantities too small to cause symptoms, and whether they would eventually cause symptoms and morbidity if untreated is unclear. Most clinicians merely observe patients with these tumors.

Adrenal adenomas < 2 cm require no special treatment but should be observed for growth or development of secretory function (such as by looking for clinical signs and periodically measuring electrolytes).

Chapter 95. Polyglandular Deficiency Syndromes

Introduction

(Autoimmune Polyglandular Syndromes; Polyendocrine Deficiency Syndromes)

Polyglandular deficiency syndromes (PDS) are characterized by sequential or simultaneous deficiencies in the function of several endocrine glands that have a common cause. Etiology is most often autoimmune. Symptoms depend on the combination of deficiencies, which fall within 1 of 3 types. Diagnosis requires measurement of hormone levels and autoantibodies against affected endocrine glands. Treatment includes replacement of missing or deficient hormones and sometimes immunosuppressants.

Etiology

Although individual endocrine glands can be damaged by numerous causes, including infection, infarction, and tumors, these syndromes usually result from an autoimmune reaction, probably triggered by a virus or other environmental antigen.

Genetic factors increase susceptibility to these syndromes, as shown by the increased presence of certain HLA subtypes in affected people and the recognition of several inheritance patterns (see Table 95-1).

Pathophysiology

The underlying autoimmune reaction involves autoantibodies against endocrine tissues, cell-mediated autoimmunity, or both and leads to inflammation, lymphocytic infiltration, and partial or complete gland destruction. More

[**Table 95-1.** Characteristics of Types I, II, and III Polyglandular Deficiency Syndromes]

than one endocrine gland is involved, although clinical manifestations are not always simultaneous. The autoimmune reaction and associated immune system dysfunction can also damage nonendocrine tissues.

Classification

Three patterns of autoimmune failure have been described (see Table 95-1), which likely reflect different autoimmune abnormalities.

Type I: Type I usually begins in childhood. The 3 primary components are

• Chronic mucocutaneous candidiasis

• Hypoparathyroidism

• Adrenal insufficiency (Addison's disease)

Candidiasis is usually the initial clinical manifestation, most often occurring in patients < 5 yr. Hypoparathyroidism occurs next, usually in patients < 10 yr. Lastly, adrenal insufficiency occurs in patients < 15 yr. Accompanying endocrine and nonendocrine disorders (see Table 95-1) continue to appear at least until patients are about age 40.

Type II (Schmidt's syndrome): Type II usually occurs in adults; peak incidence is age 30. It occurs 3 times more often in women. It typically manifests with

• Adrenal insufficiency

• Hypothyroidism or hyperthyroidism

• Type 1 diabetes (autoimmune etiology)

More rare features may also be present (see Table 95-1).

Type III: Type III is characterized by

• Glandular failure occurring in adults, particularly middle-aged women

• Hypothyroidism

• At least one of a variety of other disorders (see Table 95-1)

Type III does not involve the adrenal cortex.

Symptoms and Signs

The clinical appearance of patients with PDS is the sum of the individual endocrine deficiencies and associated nonendocrine disorders; their symptoms and signs are discussed elsewhere in THE MANUAL. The deficiencies do not always appear at the same time and may require a period of years to manifest; in such cases they do not follow a particular sequence.

Diagnosis

• Measurement of hormone levels

• Sometimes autoantibody titers

Diagnosis is suggested clinically and confirmed by detecting deficient hormone levels. Other causes of multiple endocrine deficiencies include hypothalamic-pituitary dysfunction and coincidental endocrine dysfunction due to separate causes (eg, tuberculous hypoadrenalism and nonautoimmune hypothyroidism in the same patient). Detecting autoantibodies to each affected glandular tissue can help differentiate PDS from the other causes, and elevated levels of pituitary tropic hormones (eg, thyroid-stimulating hormone) suggest the hypothalamic-pituitary axis is intact (although some patients with type II PDS have hypothalamic-pituitary insufficiency).

Because decades may pass before the appearance of all manifestations, lifelong follow-up is prudent; unrecognized hypoparathyroidism or adrenal insufficiency can be life threatening.

Relatives should be made aware of the diagnosis and screened when appropriate; measurement of glutamic acid decarboxylase antibodies may be useful in determining risk.

Treatment

• Hormone replacement

Treatment of the various individual glandular deficiencies is discussed elsewhere in THE MANUAL; the treatment of multiple deficiencies can be more complex than treatment of an isolated endocrine deficiency.

Chronic mucocutaneous candidiasis usually requires lifelong antifungal therapy (eg, oral fluconazole or ketoconazole—see p. 1103). If given early (within the first few weeks to months) in the course of endocrine failure, immunosuppressive doses of cyclosporine may benefit some patients.

IPEX Syndrome

IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) is a recessive syndrome involving aggressive autoimmunity.

This rare disorder results from mutation of the transcriptional activator, *FoxP3*, which causes regulatory T-cell dysfunction and a subsequent autoimmune disorder.

IPEX syndrome manifests as severe enlargement of the secondary lymphoid organs, type 1 diabetes mellitus, eczema, food allergies, and infections. Secondary enteropathy leads to persistent diarrhea.

Diagnosis is suggested by clinical features and confirmed by genetic analysis.

Untreated, IPEX syndrome is usually fatal in the first year of life. Immunosuppressants and bone marrow transplantation can prolong life but are rarely curative.

POEMS Syndrome

(Crow-Fukase Syndrome)

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) is a nonautoimmune polyglandular deficiency syndrome.

POEMS syndrome is probably caused by circulating immunoglobulins caused by a plasma cell dyscrasia (see also p. 1025). Circulating cytokines (IL-1-β, IL-6), vascular endothelial growth factor, and tumor necrosis factor-α are also increased.

Patients may have the following:

- Hepatomegaly
- Lymphadenopathy
- Hypogonadism
- Diabetes mellitus type 2
- Primary hypothyroidism
- Hyperparathyroidism
- Adrenal insufficiency
- Excess production of monoclonal IgA and IgG due to plasmacytomas and skin abnormalities (eg, hyperpigmentation, dermal thickening, hirsutism, angiomas, hypertrichosis)

Other symptoms and signs may include edema, ascites, pleural effusion, papilledema, and fever.

Like other syndromes of undefined pathophysiology, POEMS syndrome is diagnosed based on the constellation of symptoms and signs. Criteria include the presence of polyneuropathy and monoclonal paraproteinemia plus any 2 of the other manifestations of the disorder.

Treatment consists of chemotherapy and radiation therapy followed by autologous hematopoietic or stem cell transplantation. Five-year survival is about 60%.

Chapter 96. Porphyrias

Introduction

Porphyrias result from genetic deficiencies of enzymes of the heme biosynthetic pathway. These deficiencies allow heme precursors to accumulate, causing toxicity. Porphyrias are defined by the specific enzyme deficiency. Two major clinical manifestations occur: neurovisceral abnormalities (the acute porphyrias) and cutaneous photosensitivity (the cutaneous porphyrias).

Heme, an iron-containing pigment, is synthesized mostly in the bone marrow (by erythroblasts and reticulocytes) and is incorporated into hemoglobin. Heme is also synthesized in the liver and incorporated into certain enzymes (eg, cytochromes). Heme synthesis requires 8 enzymes (see Table 96-1). These enzymes produce and transform molecular species called porphyrins (and their precursors), which are toxic if they accumulate.

Etiology

Most porphyrias are autosomal dominant. Homozygous or double heterozygous states may be incompatible with life, generally causing fetal death; the exceptions are δ-aminolevulinic acid (ALA) dehydratase (ALAD)-deficiency porphyria and uroporphyrinogen III cosynthase deficiency, in which only homozygous or double heterozygous conditions (ie, 2 separate heterozygous mutations in the same gene in the same patient) cause disease. Disease penetrance in heterozygotes varies. In terms of genetic prevalence, the 2 most common porphyrias are acute intermittent porphyria (AIP) and porphyria cutanea tarda (PCT). The prevalence of each is about 1/10,000.

Pathophysiology

Porphyrias result from a deficiency of any of the last 7 enzymes of the heme biosynthetic pathway (deficiency of the first enzyme in the pathway, ALA synthase, causes sideroblastic anemia). Single genes encode each enzyme; any of numerous possible mutations can incapacitate the enzyme encoded by that gene. When an enzyme of heme synthesis is deficient or defective, its substrate and any other heme precursors normally modified by that enzyme may accumulate in bone marrow, liver, skin, or other tissues and have toxic effects. These precursors may appear in excess in the blood and be excreted in urine, bile, or stool.

[**Table 96-1.** Substrates and Enzymes of the Heme Biosynthetic Pathway and the Diseases Associated with their Deficiency]

Although porphyrias are most precisely defined according to the deficient enzyme, classification by major clinical features (phenotype) is often useful. Thus, porphyrias are usually divided into 2 classes:

• Acute

• Cutaneous

Acute porphyrias manifest as intermittent attacks of abdominal, mental, and neurologic symptoms. They are typically triggered by drugs and other exogenous factors. Cutaneous porphyrias tend to cause continuous or undulating symptoms involving cutaneous photosensitivity. Some acute porphyrias also have cutaneous manifestations. Because of variable penetrance in heterozygous porphyrias, clinically expressed disease is less common than genetic prevalence (see Table 96-2).

Urine discoloration (red or reddish brown) may occur in the symptomatic phase of all porphyrias except erythropoietic protoporphyria (EPP) and ALAD-deficiency porphyria. Discoloration results from oxidized porphyrins, the porphyrin

[**Table 96-2.** Major Features of the Two Most Common Porphyrias]

precursor porphobilinogen (PBG), or both. Sometimes the color develops after the urine has stood in light for about 30 min, allowing time for oxidation. In the acute porphyrias, except in ALAD-deficiency porphyria, about 1 in 3 heterozygotes (more frequently in females than males) also have increased urinary excretion of PBG (and urine discoloration) in the latent phase.

Diagnosis

Patients with symptoms suggesting porphyria are screened by blood or urine tests for porphyrins or the porphyrin precursors PBG and ALA (see Table 96-3). Abnormal results on screening are confirmed by further testing.

Asymptomatic patients, including suspected carriers and people who are between attacks, are evaluated similarly. However, the tests are less sensitive in these circumstances; measurement of RBC or WBC enzyme activity is considerably more sensitive. Genetic analysis is highly accurate and preferentially used within families when the mutation is known. Prenatal testing (involving amniocentesis or chorionic villus sampling) is possible but rarely indicated.

Acute Porphyrias

Acute porphyrias cause intermittent attacks of abdominal pain and neurologic symptoms. Attacks are precipitated by certain drugs and other factors. Patients with variegate porphyria and hereditary coproporphyria may develop

[**Table 96-3.** Screening for Porphyrias]

bullous eruptions due to sunlight exposure. Diagnosis is based on elevated levels of δ-aminolevulinic acid and porphyrin precursor porphobilinogen in the urine during attacks. Attacks are treated with glucose or, if more severe, IV heme. Symptomatic treatment, including analgesia, is given as necessary.

Acute porphyrias include, in order of prevalence, acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and the exceedingly rare δ-aminolevulinic acid dehydratase (ALAD)-deficiency porphyria.

Among heterozygotes, acute porphyrias are rarely expressed clinically before puberty and, after puberty, in only about 20 to 30%. Among homozygotes and double heterozygotes, onset generally is in childhood, and symptoms are often severe.

Precipitating Factors

Many precipitating factors exist, typically accelerating heme biosynthesis above the catalytic capacity of the defective enzyme. Accumulation of porphyrin precursor porphobilinogen (PBG) and δ-aminolevulinic acid (ALA), or in the case of ALAD-deficiency porphyria, ALA alone, results.

Hormonal factors are important. Women are more prone to attacks than men, particularly during periods of hormonal change (eg, just before menstruation, during use of oral contraceptives, during the early weeks of gestation, just after delivery). Nevertheless, pregnancy is not contraindicated.

Other factors include drugs (including barbiturates, other antiepileptic drugs, and sulfonamide antibiotics—see Table 96-4) and reproductive hormones (progesterone and related steroids), particularly those that induce hepatic ALA synthase and cytochrome P-450 enzymes. Attacks usually occur within 24 h after exposure to a precipitating drug. Low-calorie and low-carbohydrate diets, alcohol ingestion, and exposure to organic solvents can also precipitate symptoms. Infection or other illness, surgery, and mental problems are sometimes implicated. Attacks usually result from several, sometimes unidentifiable, factors.

Sunlight precipitates cutaneous symptoms in VP and HCP.

Symptoms and Signs

Symptoms and signs involve the nervous system, abdomen, or both (neurovisceral). Attacks develop over hours or days and can last

[Table 96-4. Drugs and Porphyria*]

up to several weeks. Most gene carriers experience no, or only a few, attacks in their lifetime. Others experience recurrent symptoms. In women, attacks often coincide with phases of the menstrual cycle.

The acute porphyric attack: Constipation, fatigue, irritability, and insomnia typically precede an acute attack. The most common symptoms with an attack are abdominal pain and vomiting. The pain may be excruciating and is disproportionate to abdominal tenderness. Abdominal manifestations may result from effects on visceral nerves or from local vasoconstrictive ischemia. Because there is no inflammation, the abdomen is not tender and there are no peritoneal signs. Temperature and WBC count are normal or slightly increased. Bowel distention may develop as a result of paralytic ileus. The urine is red or reddish brown and positive for PBG during an attack.

All components of the peripheral and central nervous systems may be involved. Motor neuropathy is common with severe and prolonged attacks. Muscle weakness usually begins in the extremities but can involve any motor neuron or cranial nerve and proceed to tetraplegia. Bulbar involvement can cause ventilatory failure.

CNS involvement may cause seizures or mental disturbances (eg, apathy, depression, agitation, frank psychosis, hallucinations). Seizures, psychotic behavior, and hallucinations may be due to hyponatremia or hypomagnesemia, which can also contribute to cardiac arrhythmias.

Excess catecholamines generally cause restlessness and tachycardia. Rarely, catecholamine-induced arrhythmias cause sudden death. Labile hypertension with transiently high BP may cause vascular changes progressing to irreversible hypertension if untreated. Renal failure in acute porphyria is multifactorial; acute hypertension (possibly leading to chronic hypertension) is likely a main precipitating factor.

Subacute or subchronic symptoms: Some patients have prolonged symptoms of lesser intensity (eg, obstipation, fatigue, headache, back or thigh pain, paresthesia, tachycardia, dyspnea, insomnia, mental disturbance, seizures).

Skin symptoms in VP and HCP: Fragile skin and bullous eruptions may develop on sun-exposed areas, even in the absence of neurovisceral symptoms. Often patients are not aware of the connection to sun exposure. Cutaneous manifestations are identical to those of porphyria cutanea tarda.

Late manifestations: Motor involvement during acute attacks may cause persistent weakness between attacks. Hepatocellular cancer, hypertension, and renal impairment become more common after middle age in AIP and possibly also in VP and HCP, especially in patients with previous porphyric attacks.

Diagnosis

• Urine screen for PBG

• If urine results are positive, quantitative ALA and PBG determination

• Genetic analysis if type must be identified

Acute attack: Misdiagnosis is common because the acute attack is confused with other causes of acute abdomen (sometimes leading to unnecessary surgery) or with a primary neurologic or mental disorder. However, in patients previously diagnosed as gene carriers or who have a positive family history, porphyria should be suspected. Still, even in known gene carriers, other causes must be considered.

Red or reddish brown urine, not present before onset of symptoms, is a cardinal sign and is present during full-blown attacks. A urine specimen should be examined in patients with abdominal pain of unknown cause, especially if severe constipation, vomiting, tachycardia, muscle weakness, bulbar involvement, or mental symptoms occur.

If porphyria is suspected, the urine is analyzed for PBG using a rapid qualitative or semiquantitative determination. A positive result or high clinical suspicion necessitates quantitative ALA and PBG measurements preferentially obtained from the same specimen. PBG and ALA levels > 5 times normal indicate an acute porphyric attack unless patients are gene carriers in whom porphyrin precursor excretion occurs at similar levels even during the latent phase of the disorder.

If urinary PBG and ALA levels are normal, an alternative diagnosis must be considered. Elevated ALA with normal or slightly increased PBG suggests lead poisoning or ALAD-deficiency porphyria. Analysis of a 24-h urine specimen is not useful. Instead, a random urine specimen is used, and PBG and ALA levels are corrected for dilution by relating to the creatinine level of the sample. Electrolytes and Mg should be measured. Hyponatremia may be present because of excessive vomiting or diarrhea after hypotonic fluid replacement or because of the syndrome of inappropriate ADH secretion (SIADH).

Determination of type: Because treatment does not depend on the type of acute porphyria, identification of the specific type is valuable mainly for finding gene carriers among relatives. When the type and mutation are already known from previous testing of relatives, the diagnosis is clear but may be confirmed by gene analysis. Enzymatic diagnosis is not necessary. If there is no family history to guide the diagnosis, the different forms of acute porphyria are distinguished by characteristic patterns of porphyrin (and precursor) accumulation and excretion in plasma, urine, and stool. When urine analysis reveals increased levels of ALA and PBG, fecal porphyrins may be measured. Fecal porphyrins are usually normal or minimally increased in AIP but elevated in HCP and VP. Often, these markers are not present in the quiescent phase of the disorder. In HCP and VP, plasma porphyrins with characteristic fluorescence are sought. RBC PBG deaminase levels that are about 50% of normal suggest AIP. Diminished WBC protoporphyrinogen oxidase levels suggest VP, and diminished coproporphyrinogen oxidase levels suggest HCP.

Family studies: Children of a gene carrier have a 50% risk of inheriting the disorder. Because diagnosis followed by counseling reduces the risk of morbidity, children in affected families should be tested before the onset of puberty. Genetic testing is used if the mutation has been identified in the index case. If not, pertinent RBC or WBC enzyme levels are measured. Gene analysis can be used for in utero diagnosis (using amniocentesis or chorionic villus sampling) but is seldom indicated because of the favorable outlook for most gene carriers.

Prognosis

Advances in medical care and self-care have improved the prognosis for symptomatic patients. Still, some patients develop recurrent crises or progressive disease with permanent paralysis or renal failure. Also, frequent need for potent analgesics may give rise to drug addiction.

Treatment

- Triggers eliminated if possible
- Dextrose (oral or IV)
- IV heme

Treatment of the acute attack is identical for all the acute porphyrias. Possible triggers (eg, drugs) are identified and eliminated. Unless the attack is mild, patients are hospitalized in a darkened, quiet, private room. Heart rate, BP, and fluid and electrolyte balance are monitored. Neurologic status, bladder function, muscle and tendon function, respiratory function, and pulse oximetry are continuously monitored. Symptoms (eg, pain, vomiting) are treated with nonporphyrinogenic drugs as needed (see Table 96-4).

Dextrose 300 to 500 g daily inhibits ALA synthase and relieves symptoms. It can be given by mouth if patients are not vomiting; otherwise, it is given IV. To avoid overhydration with consequent hyponatremia, 1 L of a 50% dextrose solution can be given by central venous catheter over 24 h.

IV heme is more effective than dextrose and should be given immediately in severe attacks, electrolyte imbalance, or muscle weakness. Heme usually resolves symptoms in 3 to 4 days. If heme therapy is delayed, nerve damage is more severe and recovery is slower and possibly incomplete. Heme is available in the US as lyophilized hematin to be reconstituted in a glass vial with sterile water. The dose is 3 mg/kg IV once/day for 4 days. In this form, heme degradation products form rapidly and may cause phlebitis at the infusion site; they also have a transient anticoagulant effect. Adverse effects can be reduced by reconstitution with, eg, 20% human albumin. Heme arginate is a more stable, generally toxicity-free alternative.

In patients with severe recurrent attacks, who are at risk of renal damage or permanent neurologic damage, liver transplantation is an option. Renal transplantation, with or without simultaneous liver exchange, should be considered in patients with active disease and terminal renal failure, because there is considerable risk that nerve damage will progress at the start of dialysis.

Prevention

Carriers of acute porphyria should avoid the following:

• Potentially harmful drugs (see Table 96-4)

• Alcohol

• Emotional stress

• Exposure to organic solvents (eg, in painting or dry cleaning)

• Crash diets

• Periods of starvation

Diets for obesity should provide gradual weight loss and be adopted only during periods of remission. Carriers of VP or HCP should minimize sun exposure; sunscreens that block only ultraviolet B light are ineffective, but opaque titanium dioxide preparations are beneficial. Support associations for porphyria patients can provide written information and direct counseling.

Patients should be identified prominently in the medical record as carriers and should carry a card verifying the carrier state and precautions to be observed.

A high-carbohydrate diet may decrease the risk of acute attacks. A high-carbohydrate diet or a lump of sugar every hour may help relieve symptoms of an acute attack. Prolonged use should be avoided in order to decrease risk of obesity and dental caries.

Patients who experience recurrent and predictable attacks (typically women with attacks related to the menstrual cycle) may benefit from prophylactic heme therapy given shortly before the expected onset. There is no standardized regimen; a specialist should be consulted. Frequent premenstrual attacks in some women are aborted by administration of a gonadotropin-releasing hormone analog plus low-dose estrogen. Oral contraceptives are sometimes used successfully, but the progestin component is likely to exacerbate the porphyria.

To prevent renal damage, chronic hypertension is treated (using safe drugs). Patients with evidence of impaired renal function are referred to a nephrologist.

The incidence of hepatocellular cancer is high among carriers of acute porphyria, especially in patients

with active disease. Patients who are > 50 should undergo yearly or twice yearly surveillance, including liver screening with contrast-enhanced ultrasonography. Early intervention can be curative and increases life expectancy.

Cutaneous Porphyrias

Cutaneous porphyrias tend to manifest as undulating or unremitting disease with a relatively steady production of phototoxic porphyrins in the liver or bone marrow. These porphyrins accumulate in the skin and, on sunlight exposure (visible light, including near-ultraviolet [UV]), generate cytotoxic radicals that cause cutaneous manifestations.

Cutaneous porphyrias include porphyria cutanea tarda, erythropoietic protoporphyria (EPP), and the extremely rare hepatoerythropoietic porphyria and congenital erythropoietic porphyria (see Table 96-5). The acute porphyrias variegate porphyria and hereditary coproporphyria also have cutaneous manifestations.

In all cutaneous porphyrias except EPP, cutaneous photosensitivity manifests as fragile skin and bullous eruptions. Skin changes generally occur on sun-exposed areas (eg, face, neck, dorsal sides of fingers and hands) or traumatized skin. The cutaneous reaction is

[**Table 96-5.** Some Less Common Porphyrias]

insidious, and often patients are unaware of the connection to sun exposure. In contrast, the photosensitivity in EPP occurs within minutes or hours after sun exposure, manifesting as a burning pain that persists for hours, often without any objective signs on the skin.

Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is a comparatively common porphyria affecting mainly the skin. Liver disease is common. Symptoms include fragile skin and blisters affecting sun-exposed areas. Iron plays a key role in pathogenesis. Several environmental factors lower the threshold for the phototoxic skin reaction, including alcohol ingestion, estrogens, hepatitis C infection, and possibly HIV infection. Drugs, with the exceptions of iron and estrogens, are not triggers. Diagnosis is by porphyrin analysis of urine and stool. Differentiation from the acute cutaneous porphyrias hereditary coproporphyria and variegate porphyria is important. Treatment includes iron depletion by phlebotomy and forced porphyrin excretion by treatment with chloroquine. Prevention is by avoidance of sunlight, alcohol, estrogens, and iron-containing drugs.

Pathophysiology

PCT results from hepatic deficiency of uroporphyrinogen decarboxylase (UPGD—see Table 96-1). In about 80% of patients, the responsible mutation is sporadic; the remaining 20% are hereditary.

Porphyrins accumulate in the liver and are transported to the skin, where they cause photosensitivity. The 50% decrease in UPGD activity in heterozygous patients is insufficient to cause clinical PCT. Other factors must further impair enzyme activity. Iron plays a central role, probably by generating oxygen radicals that inhibit UPGD by oxidizing its substrate; thus, hemochromatosis is a significant risk factor. Alcohol, estrogens, and chronic viral infection probably contribute in different ways by increasing iron activity in hepatic tissue. The drugs that commonly trigger acute porphyria (see Table 96-4) do not trigger PCT.

Liver disease is common in PCT and may be due partly to porphyrin accumulation, chronic hepatitis C infection, concomitant hemosiderosis, or excess alcohol ingestion. Cirrhosis occurs in ≤ 35% of patients, and hepatocellular carcinoma occurs in 7 to 24% (more common among middle-aged men).

The 2 major forms of the disease, types 1 and 2, have the same precipitants, symptoms, and treatment. Overall prevalence may be on the order of 1/10,000.

In type 1 PCT (sporadic), decarboxylase deficiency is restricted to the liver and no genetic background is recognized. It usually manifests in middle age or later.

In type 2 PCT (familial), decarboxylase deficiency is inherited in an autosomal dominant fashion with limited penetrance. Prevalence is lower than in sporadic PCT. Deficiency occurs in all cells, including RBCs. It may develop earlier than type 1, occasionally in childhood.

Secondary PCT-like conditions (pseudoporphyria) may occur with certain photosensitizing drugs (eg, furosemide, tetracyclines, sulfonamides, some NSAIDs). Because porphyrins are poorly dialyzed, some patients receiving long-term hemodialysis develop a skin condition that resembles PCT; this condition is termed pseudoporphyria of end-stage renal disease.

Symptoms and Signs

Patients present with fragile skin, mainly on sun-exposed areas. Phototoxicity is delayed: patients do not always connect sun exposure with symptoms.

Spontaneously or after minor trauma, tense bullae develop. Accompanying erosions and ulcers may develop secondary infection; they heal slowly, leaving atrophic scars. Sun exposure occasionally leads to erythema, edema, or itching. Hyperemic conjunctivitis may develop, but other mucosal sites are not affected. Areas of hypopigmentation or hyperpigmentation may develop, as may facial hypertrichosis and pseudosclerodermoid changes.

Diagnosis

- Levels of plasma porphyrins, urinary uroporphyrin and heptacarboxyl porphyrin, and fecal isocoproporphyrin

In otherwise healthy patients, fragile skin and blister formation suggest PCT. Differentiation from acute porphyrias with cutaneous symptoms (variegate porphyria [VP] and hereditary coproporphyria [HCP]) is important because in patients with VP and HCP, the erroneous prescription of porphyrogenic drugs may trigger the severe neurovisceral symptoms of the acute porphyrias. Previous unexplained neurologic symptoms or abdominal pain may suggest an acute porphyria. A history of exposure to chemicals that can cause pseudoporphyria should be sought.

Although all porphyrias that cause skin lesions are accompanied by elevated plasma porphyrins, elevated urinary uroporphyrin and heptacarboxyl porphyrin and fecal isocoproporphyrin indicate PCT. Urine levels of porphyrin precursor porphobilinogen (PBG) and, usually, δ-aminolevulinic acid (ALA) are normal in PCT. RBC activity of UPGD is normal in type 1 PCT but decreased in type 2.

Because concurrent hepatitis C infection is common and may be asymptomatic, serum markers for hepatitis C (see p. 253) should be investigated.

Treatment

Two different therapeutic strategies are available:

- Reduction of body iron stores

- Increase in porphyrin excretion

These strategies can be combined for more rapid remission. The treatment is monitored by determinations of urinary porphyrin excretion every other or every 3rd month until full remission.

Iron removal by phlebotomy is usually effective. A pint of blood is removed every 2nd or every 3rd week; shorter intervals unnecessarily risk causing anemia. When serum ferritin falls slightly below normal, phlebotomy is stopped. Usually, only 5 to 6 sessions are needed. Urine and plasma porphyrins fall

gradually with treatment, lagging behind but paralleling the fall in ferritin. The skin eventually becomes normal. After remission, further phlebotomy is needed only if there is a recurrence.

Low-dose chloroquine or hydroxychloroquine (100 to 125 mg po twice/wk) removes excess porphyrins from the liver by increasing the excretion rate. Higher doses can cause transient liver damage and worsening of porphyria. When remission is achieved, the regimen is stopped.

Chloroquine and hydroxychloroquine are not effective in advanced renal disease, and phlebotomy is usually contraindicated because of underlying anemia. However, recombinant erythropoietin mobilizes excess iron and resolves the anemia enough to permit phlebotomy. In end-stage renal disease, deferoxamine is an adjunct to phlebotomy for reduction of hepatic iron, the complexed iron being removed during dialysis. Dialyzers with ultrapermeable membranes and extra high blood flow rates are needed.

Patients with overt PCT and hepatitis C infection are preferentially treated with pegylated interferon alfa-2a and ribavirin. Previous iron depletion augments the response to antiviral therapy.

Children with symptomatic PCT are treated with small-volume phlebotomies or oral chloroquine; dosage is determined by body weight.

Skin symptoms occurring during pregnancy are treated with phlebotomy. In refractory cases, low-dose chloroquine can be added; no teratogenic effects have been recognized. Depending on degree of hemodilution and iron depletion, the skin symptoms usually abate as pregnancy advances.

Postmenopausal estrogen supplementation is interrupted during treatment for PCT. Stopping estrogens often induces remission. After remission, estrogens can be reintroduced, preferentially in transdermal administration to reduce hepatic porphyrogenic exposure.

Prevention

Patients should avoid sun exposure; hats and clothing protect best, as do zinc or titanium oxide sunscreens. Typical sunscreens that block UV light are ineffective, but UVA-absorbing sunscreens, such as those containing dibenzylmethanes, may help somewhat. Alcohol ingestion should be avoided permanently, but estrogen supplementation can usually be resumed safely after a disease remission.

Erythropoietic Protoporphyria

Erythropoietic protoporphyria (EPP) typically manifests in infancy with burning skin pain after even short exposure to sunlight. Gallstones are common later in life, and acute liver failure occurs in about 10%. Diagnosis is based on symptoms and increased levels of protoporphyrin in RBCs and plasma. Treatment is with β-carotene or dihydroxyacetone and avoidance of sunlight. In patients with liver failure, combined liver and bone marrow transplantation may be life saving as well as curative.

Etiology

EPP results from deficiency of the enzyme ferrochelatase in erythroid tissue. Clinical prevalence is about1/75,000. Phototoxic protoporphyrins accumulate in bone marrow and RBCs, enter the plasma, and are deposited in the skin or excreted by the liver into bile and stool. Heavy biliary protoporphyrin excretion can cause gallstones. These cytotoxic molecules sometimes damage the hepatobiliary tract, resulting in hepatic protoporphyrin accumulation that leads to acute liver failure; liver failure may become clinically acute within days.

Inheritance pattern is basically autosomal dominant but complex. Clinical manifestations occur only in people who have both the defective EPP gene and an unusual low-output (but otherwise normal) allele from the healthy parent.

Symptoms and Signs

Severity varies greatly, even among patients within a single family. Usually, an infant or young child with EPP cries for hours after even short exposure to sun. However, because cutaneous signs are usually absent and young children cannot describe their symptoms, EPP often goes undiagnosed.

If unrecognized, EPP causes psychosocial problems because children inexplicably refuse to go outdoors. The pain may be so distressing that it causes nervousness, tenseness, aggressiveness, or even feelings of detachment from the surroundings or suicidal thoughts.

During childhood, crusting may develop around the lips and on the back of the hands after prolonged sun exposure. Blistering and scarring do not occur. If skin protection is chronically neglected, rough, thickened, and leathery skin may develop, especially over the knuckles. Linear perioral furrows (carp mouth) may develop.

Biliary excretion of large amounts of protoporphyrin can cause cholestasis that progresses to nodular cirrhosis and acute liver failure in ≤ 10% of patients; symptoms include jaundice, malaise, upper abdominal pain, and tender hepatic enlargement.

Diagnosis

• RBC and plasma protoporphyrin measurement

EPP should be suspected in children and adults with painful cutaneous photosensitivity who experience no blisters or scarring. Family history is usually negative. The diagnosis is confirmed by finding increased RBC and plasma protoporphyrin levels. A genetic marker for susceptibility to cholestatic complications has been identified.

Screening of potential carriers among relatives is by showing increased RBC protoporphyrin contents and decreased ferrochelatase activity (assayed in lymphocytes) or by genetic testing if the mutation has been identified in the index case. Susceptibility for cutaneous disease in carriers is indicated by finding the low-output ferrochelatase allele.

Treatment

• Avoidance of triggers (eg, sun exposure, alcohol, fasting)

• Symptomatic treatment

• Sometimes oral β-carotene

Acute skin symptoms are alleviated by cold baths or wet towels, analgesics, and antihistamines. Regular physician-patient consultations that provide information, discussion, and opportunities for genetic counseling together with physical checkups are important.

Patients should avoid sun exposure; opaque titanium dioxide or zinc oxide sunscreens are beneficial, and UVA-absorbing sunscreens, such as those containing dibenzylmethanes, may help somewhat. Protection against the operating light is strictly required in liver transplantation to avoid serious phototoxic injury to inner organs. Covering of light sources with filters that block wavelengths < 470 nm is required. Endoscopy, laparoscopy, and nontransplant abdominal surgery are not connected with risk of phototoxic damage.

[
Table 96-6. Doses of β-Carotene in Erythropoietic Protoporphyria]

Patients should avoid alcohol and fasting, both of which increase the rate of RBC production and thus the protoporphyrin load. Drugs that trigger acute porphyrias (see Table 96-4) need not be avoided.

Systemic β-carotene causes slight yellow protective skin coloration and neutralizes the toxic radicals in the skin that cause symptoms. Dose depends on patient age (see Table 96-6).

Another antioxidant, cysteine, may also lessen photosensitivity. The brown protective skin color obtained with topically applied dihydroxyacetone is generally cosmetically preferable to the yellowish tint caused by β-carotene.

If the above-mentioned measures are ineffective (eg, patients have increasing photosensitivity, rising porphyrin levels, or progressive jaundice), RBC hypertransfusion (ie, to abovenormal Hb levels) can reduce the production rate of porphyrin-loaded RBCs. Administration of bile acids facilitates biliary excretion of protoporphyrin. Oral cholestyramine or charcoal interrupts the enterohepatic circulation. Liver failure may require immediate liver transplantation. Bone marrow exchange corrects the basic metabolic defect.

Patients with EPP should undergo annual surveillance for risks of cholestasis. Tests include RBC porphyrin levels, porphyrin excretion patterns, and liver function. Abnormal findings should be evaluated by a porphyria specialist and a hepatologist. If the liver appears involved, biopsy is done to identify progressive disease. Patients should be vaccinated against hepatitis A and B and advised to avoid alcohol.

Chapter 97. Fluid and Electrolyte Metabolism

Introduction

Body fluid volume and electrolyte concentration are normally maintained within very narrow limits despite wide variations in dietary intake, metabolic activity, and environmental stresses. Homeostasis of body fluids is preserved primarily by the kidneys.

Water and Sodium Balance

Water and Na balance are closely interdependent. Total body water (TBW) is about 60% of body weight (ranging from about 50% in obese people to 70% in lean people). Almost two thirds of TBW is in the intracellular compartment (intracellular fluid, or ICF); the other one third is extracellular (extracellular fluid, or ECF). Normally, about 25% of the ECF is in the intravascular compartment; the other 75% is interstitial fluid (see
Fig. 97-1).

The major intracellular cation is K, with an average concentration of 140 mEq/L. The extracellular K concentration is 3.5 to 5 mEq/L. The major extracellular cation is Na, with an average concentration of 140 mEq/L and an intracellular Na concentration of 12 mEq/L.

Osmotic forces: The concentration of combined solutes in water is osmolarity (amount of solute per L of solution), which, in body fluids, is similar to osmolality (amount of solute per kg of solution). Plasma osmolality can be measured in the laboratory or estimated according to the formula

Plasma osmolality (mOsm/kg) =

$$2[\text{serum Na}] + \frac{[\text{Glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

where serum Na is expressed in mEq/L and glucose and BUN are expressed in mg/dL. Osmolality of body fluids is normally between 275 and 290 mOsm/kg. Na is the major determinant of serum osmolality. Apparent changes in osmolality may result from errors in the measurement of Na with electrodes that are not ion selective (see under Diagnosis on p. 826). An osmolar gap is present when measured osmolality exceeds estimated osmolality by ≥ 10 mOsm/kg. It is caused by unmeasured osmotically active substances present in the plasma. The most common are alcohols (ethanol, methanol, isopropanol, ethylene glycol), mannitol, and glycine.

Water crosses cell membranes freely from areas of low solute concentration to areas of high solute concentration. Thus, osmolality tends to equalize across the various body fluid compartments, resulting primarily from movement of water, not solutes. Solutes such as urea that freely diffuse across cell membranes have little or no effect on water shifts (little or no osmotic activity), whereas solutes that are restricted primarily to one fluid compartment, such as Na and K, have the greatest osmotic activity. Tonicity, or effective osmolality, reflects osmotic activity and determines the force drawing water across fluid compartments (the osmotic force). Osmotic force can be opposed by other forces. For example, plasma proteins have a small osmotic effect that tends to draw water into the plasma; this osmotic effect is normally counteracted by vascular hydrostatic forces that drive water out of the plasma.

Water intake and excretion: The average daily fluid intake is about 2.5 L. The amount needed to replace losses from the urine and other sources is about 1 to 1.5 L/day in healthy adults. However, on a short-term basis, an average

[**Fig. 97-1.** Fluid compartments in an average 70-kg man.]

young adult with normal kidney function may ingest as little as 200 mL of water each day to excrete the nitrogenous and other wastes generated by cellular metabolism. More is needed in people with any loss of renal concentrating capacity. Renal concentrating capacity is lost in

- The elderly
- People with diabetes insipidus, certain renal disorders, hypercalcemia, severe salt restriction, chronic overhydration, or hyperkalemia
- People who ingest ethanol, phenytoin, lithium, demeclocycline, or amphotericin B
- People with osmotic diuresis (eg, due to high-protein diets or hyperglycemia)

Other obligatory water losses are mostly insensible losses from the lungs and skin, averaging about 0.4 to 0.5 mL/kg/h or about 650 to 850 mL/day in a 70-kg adult. With fever, another 50 to 75 mL/day may be lost for each degree C of temperature elevation above normal. GI losses are usually negligible, except when marked vomiting, diarrhea, or both occur. Sweat losses can be significant during environmental heat exposure or excessive exercise.

Water intake is regulated by thirst. Thirst is triggered by receptors in the anterolateral hypothalamus that respond to increased serum osmolality (as little as 2%) or decreased body fluid volume. Rarely hypothalamic dysfunction decreases the capacity for thirst.

Water excretion by the kidneys is regulated primarily by ADH (vasopressin). ADH is released by the posterior pituitary and results in increased water reabsorption in the distal nephron. ADH release is stimulated by any of the following:

- Increased serum osmolality
- Decreased blood volume
- Decreased BP
- Stress

ADH release may be impaired by certain substances (eg, ethanol, phenytoin) and central diabetes insipidus (see p. 772).

Water intake decreases serum osmolality. Low serum osmolality inhibits ADH secretion, allowing the kidneys to produce dilute urine. The diluting capacity of healthy kidneys in young adults is such that maximum daily fluid intake can be as much as 25 L; greater amounts quickly lower serum osmolality.

Disorders of Fluid Volume

Because Na is the major osmotically active ion in the ECF, total body Na content determines ECF volume. Deficiency or excess of total body Na content causes ECF volume depletion or overload. Plasma Na concentration does not necessarily reflect total body Na.

Dietary intake and renal excretion regulate total body Na content. When total Na content and ECF volume are low, the kidneys increase Na conservation. When total Na content and ECF volume are high, Na excretion (natriuresis) increases so that volume decreases.

Renal Na excretion can be adjusted widely to match Na intake. Renal Na excretion requires delivery of Na to the kidneys and so depends on renal blood flow and GFR. Thus, inadequate Na excretion may be secondary to decreased renal blood flow, as in chronic kidney disease or heart failure.

Renin-angiotensin-aldosterone axis: The renin-angiotensin-aldosterone axis is the main regulatory mechanism of renal Na excretion. In volume-depleted states, GFR and Na delivery to the distal nephrons decreases, causing release of renin. Renin cleaves angiotensinogen (renin substrate) to form angiotensin I. ACE then cleaves angiotensin I to angiotensin II. Angiotensin II does the following:

- Increases Na retention by decreasing the filtered load of Na and enhancing proximal tubular Na

reabsorption.

- Increases BP (has pressor activity)
- Increases thirst
- Directly impairs water excretion
- Stimulates the adrenal cortex to secrete aldosterone, which increases Na reabsorption via multiple renal mechanisms

Angiotensin I can also be transformed to angiotensin III, which stimulates aldosterone release as much as angiotensin II but has much less pressor activity. Aldosterone release is also stimulated by hyperkalemia.

Other natriuretic factors: Several other natriuretic factors have been identified, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and a C-type natriuretic peptide (CNP).

ANP is secreted by cardiac atrial tissue. Concentration increases in response to ECF volume overload (eg, heart failure, chronic kidney disease, cirrhosis with ascites) and primary aldosteronism and in some patients with primary hypertension. Decreases have occurred in the subset of patients with nephrotic syndrome who have presumed ECF volume contraction. High concentrations increase Na excretion and increase GFR even when BP is low.

BNP is synthesized mainly in the atria and left ventricle and has similar triggers and effects to ANP. BNP assays are readily available. High BNP concentration is used to diagnose volume overload.

CNP, in contrast to ANP and BNP, is primarily vasodilatory.

Na depletion and excess: Na depletion requires inadequate Na intake plus abnormal losses from the skin, GI tract, or kidneys (defective renal Na conservation). Defective renal Na conservation may be caused by primary renal disease, adrenal insufficiency, or diuretic therapy.

Na overload requires higher Na intake than excretion; however, because normal kidneys can excrete large amounts of Na, Na overload generally reflects defective regulation of renal blood flow and Na excretion (eg, as occurs in heart failure, cirrhosis, or chronic kidney disease).

Volume Depletion

Volume depletion, or ECF volume contraction, occurs as a result of loss of total body Na. Causes include vomiting, excessive sweating, diarrhea, burns, diuretic use, and kidney failure. Clinical features include diminished skin turgor, dry mucous membranes, tachycardia, and orthostatic hypotension. Diagnosis is clinical. Treatment involves administration of Na and water.

Because water crosses plasma membranes in the body through passive osmosis, loss of the major extracellular cation (Na) quickly results in water loss from the ECF space as well. In this way, Na loss always causes water loss. However, depending on many factors, serum Na concentration can be high, low, or normal in volume-depleted patients (despite the decreased total body Na content). ECF volume is related to effective circulating volume. A decrease in ECF (hypovolemia) generally causes a decrease in effective circulating volume, which in turn causes decreased organ perfusion and leads to clinical sequelae. Common causes of volume depletion are listed in Table 97-1.

Symptoms and Signs

In mild volume depletion (< 5% of ECF), the only sign may be diminished skin turgor (best assessed at the upper torso). Skin turgor may be low in elderly patients regardless of volume status. Patients may complain of thirst. Dry mucous membranes do not always correlate with volume depletion, especially in

the elderly and in mouth-breathers. Oliguria is typical.

When ECF volume has diminished by 5 to 10%, orthostatic tachycardia, hypotension, or both are usually, but not always, present. Also, orthostatic changes can occur in patients without ECF volume depletion, particularly patients deconditioned or bedridden. Skin turgor may decrease further.

[Table 97-1. Common Causes of Volume Depletion]

When fluid loss exceeds 10% of ECF volume, signs of shock can occur (eg, tachypnea, tachycardia, hypotension, confusion, poor capillary refill).

Diagnosis

• Clinical findings

• Sometimes serum electrolytes, BUN, and creatinine

• Rarely serum osmolality and urine chemistries

Volume depletion is suspected in patients at risk, most often in patients with a history of inadequate fluid intake (especially in comatose or disoriented patients), increased fluid losses, diuretic therapy, and renal or adrenal disorders.

Diagnosis is usually clinical. When the cause is obvious and easily correctable (eg, acute gastroenteritis in otherwise healthy patients), laboratory testing is unnecessary; otherwise, serum electrolytes, BUN, and creatinine are measured. Serum osmolality and urine Na, creatinine, and osmolality are measured when there is suspicion of clinically meaningful electrolyte abnormality that is not clear from serum tests and for patients with cardiac or renal disease. When metabolic alkalosis is present, urine Cl is also measured.

Central venous pressure and pulmonary artery occlusion pressure are decreased in volume depletion, but measurement is rarely required. Measurement, which requires an invasive procedure, is occasionally necessary for patients for whom even small amounts of added volume may be detrimental, such as those with unstable heart failure or advanced chronic kidney disease.

The following concepts are helpful when interpreting urine electrolyte and osmolality values:

• During volume depletion, normally functioning kidneys conserve Na. Thus, the urine Na concentration is usually < 15 mEq/L; the fractional excretion of Na (urine Na/serum Na divided by urine creatinine/serum creatinine) is usually < 1%; also, urine osmolality is often > 450 mOsm/kg.

• When metabolic alkalosis is combined with volume depletion, urine Na concentration may be high because large amounts of HCO_3 are spilled in the urine, obligating the excretion of Na to maintain electrical neutrality. In this instance, a urine Cl concentration of < 10 mEq/L more reliably indicates volume depletion.

• Misleadingly high urinary Na (generally > 20 mEq/L) or low urine osmolality can also occur due to renal Na losses resulting from renal disease, diuretics, or adrenal insufficiency.

Volume depletion frequently increases the BUN and serum creatinine concentrations with the ratio of BUN to creatinine often > 20:1. Values such as Hct often increase in volume depletion but are difficult to interpret unless baseline values are known.

Treatment

• Replacement of Na and water

The cause of volume depletion is corrected and fluids are given to replace existing volume deficits as well as any ongoing fluid losses and to provide daily fluid requirements. Mild-to-moderate volume deficits may

be replaced by increased oral intake of Na and water when patients are conscious and not vomiting. When volume deficits are severe or when oral fluid replacement is impractical, IV 0.9% saline is given. Typical IV regimens are discussed on p. 2297; oral regimens are discussed on p. 2809.

Volume Overload

Volume overload generally refers to expansion of the ECF volume. ECF volume expansion typically occurs in heart failure, nephrotic syndrome, and cirrhosis. Renal Na retention leads to increased total body Na content. This increase results in varying degrees of volume overload. In heart failure, the increased ECF volume results in decreased effective circulating volume, which in turn causes decreased organ perfusion leading to clinical sequelae. Serum Na concentration can be high, low, or normal in volume-overloaded patients (despite the increased total body Na content).

An increase in total body Na is the key pathophysiologic event. It increases osmolality, which triggers compensatory mechanisms that cause water retention. When sufficient fluid accumulates in the ECF (usually > 2.5 L), edema (see p. 2031) develops.

Among the most common causes of ECF volume overload are the following:

• Heart failure

• Cirrhosis

• Renal failure

• Nephrotic syndrome

• Premenstrual edema

• Pregnancy

Clinical features include weight gain and edema. Diagnosis is clinical. Treatment aims to correct the cause.

Hyponatremia

Hyponatremia is decrease in serum Na concentration < 136 mEq/L caused by an excess of water relative to solute. Common causes include diuretic use, diarrhea, heart failure, and renal disease. Clinical manifestations are primarily neurologic (due to an osmotic shift of water into brain cells causing edema), especially in acute hyponatremia, and include headache, confusion, and stupor; seizures and coma may occur. Diagnosis is by measuring serum Na. Serum and urine electrolytes and osmolality help determine the cause. Treatment involves restricting water intake and promoting its loss, replacing any Na deficit, and treating the cause.

Etiology

Hyponatremia reflects an excess of total body water (TBW) relative to total body Na content. Because total body Na content is reflected by ECF volume status, hyponatremia must be considered along with status of the ECF volume: hypovolemia, euvolemia, and hypervolemia (see Table 97-2). Note that the ECF volume is not the same as effective plasma volume. For example, decreased effective plasma volume may occur with decreased ECF volume, but it may also occur with an increased ECF volume (eg, in heart failure, hypoalbuminemia, or capillary leak syndrome).

Hypovolemic hyponatremia: Deficiencies in both TBW and total body Na exist, although proportionally more Na than water has been lost; the Na deficit causes hypovolemia. In hypovolemic hyponatremia, both serum osmolality and blood volume decrease. ADH secretion increases despite a decrease in osmolality

to maintain blood volume. The resulting water retention increases plasma dilution and hyponatremia.

[**Table 97-2.** Principal Causes of Hyponatremia]

Extrarenal fluid losses, such as those that occur with the losses of Na-containing fluids as in protracted vomiting, severe diarrhea, or sequestration of fluids in a 3rd space (see Table 97-3), can cause hyponatremia typically when losses are replaced by ingesting plain water or liquids low in Na (see Table 97-4) or by hypotonic IV fluid. Significant ECF fluid losses also cause release of ADH, causing water retention by the kidneys, which can maintain or worsen hyponatremia. In extrarenal causes of hypovolemia, because the normal renal response to volume loss is Na conservation, urine Na concentration is typically < 10 mEq/L.

Renal fluid losses resulting in hypovolemic hyponatremia may occur with mineralocorticoid deficiency, diuretic therapy, osmotic diuresis, or salt-losing nephropathy. Salt-losing nephropathy encompasses a loosely defined group of intrinsic renal disorders with primarily renal tubular dysfunction. This group includes interstitial nephritis, medullary cystic disease, partial urinary tract obstruction, and, occasionally, polycystic kidney disease. Renal causes of hypovolemic hyponatremia can usually be differentiated from extrarenal causes by the history. Patients with ongoing renal fluid losses can also be distinguished from patients with extrarenal fluid losses because the urine Na concentration is inappropriately high (> 20 mEq/L). Urine Na concentration may not help in differentiation when metabolic alkalosis (as occurs with protracted vomiting) is present and large amounts of HCO_3 are spilled in the urine, obligating the excretion of Na to maintain electrical neutrality. In metabolic alkalosis, urine Cl concentration frequently differentiates renal from extrarenal sources of volume depletion (see p. 862).

[**Table 97-3.** Composition of Body Fluids]

[**Table 97-4.** Approximate Na Content of Common Beverages]

Diuretics may also cause hypovolemic hyponatremia. Thiazide diuretics, in particular, decrease the kidneys' diluting capacity and increase Na excretion. Once volume depletion occurs, the nonosmotic release of ADH causes water retention and worsens hyponatremia. Concomitant hypokalemia shifts Na intracellularly and enhances ADH release, thereby worsening hyponatremia. This effect of thiazides may last for up to 2 wk after cessation of therapy; however, hyponatremia usually responds to replacement of K and volume deficits along with judicious monitoring of water intake until the drug effect dissipates. Elderly patients may have increased Na diuresis and are especially susceptible to thiazide-induced hyponatremia, particularly when they have a preexisting defect in renal capacity to excrete free water. Rarely, such patients develop severe, life-threatening hyponatremia within a few weeks after the initiation of a thiazide diuretic. Loop diuretics much less commonly cause hyponatremia.

Euvolemic hyponatremia: In euvolemic (dilutional) hyponatremia, total body Na and thus ECF volume are normal or near-normal; however, TBW is increased.

Primary polydipsia can cause hyponatremia only when water intake overwhelms the kidneys' ability to excrete water. Because normal kidneys can excrete up to 25 L urine/day, hyponatremia due solely to polydipsia results only from the ingestion of large amounts of water or from defects in renal capacity to excrete free water. Patients affected include those with psychosis or more modest degrees of polydipsia plus renal insufficiency.

Euvolemic hyponatremia may also result from excessive water intake in the presence of Addison's disease, hypothyroidism, or nonosmotic ADH release (eg, due to stress; postoperative states; use of drugs such as chlorpropamide, tolbutamide, opioids, barbiturates, vincristine, clofibrate, or carbamazepine). Postoperative hyponatremia most commonly occurs because of a combination of nonosmotic ADH release and excessive administration of hypotonic fluids after surgery. Certain drugs (eg, cyclophosphamide, NSAIDs, chlorpropamide) potentiate the renal effect of endogenous ADH, whereas others (eg, oxytocin) have a direct ADH-like effect on the kidneys. A deficiency in water excretion is common in all these conditions. Diuretics can cause or contribute to euvolemic hyponatremia if another factor causes water retention or excessive water intake. The syndrome of inappropriate ADH secretion

(SIADH—see Sidebar 97-1) is another cause of euvolemic hyponatremia.

Hypervolemic hyponatremia: Hypervolemic hyponatremia is characterized by an increase in both total body Na (and thus ECF volume) and TBW with a relatively greater increase in TBW. Various edematous disorders, including heart failure and cirrhosis, cause hypervolemic hyponatremia. Rarely, hyponatremia occurs in nephrotic syndrome, although pseudohyponatremia may be due to interference with Na measurement by elevated lipids. In each of these disorders, a decrease in effective circulating volume results in the release of ADH and angiotensin II. The following factors contribute to hyponatremia:

• The antidiuretic effect of ADH on the kidneys

• Direct impairment of renal water excretion by angiotensin II

• Decreased GFR

• Stimulation of thirst by angiotensin II

Urine Na excretion is usually < 10 mEq/L, and urine osmolality is high relative to serum osmolality.

Hyponatremia in AIDS: Hyponatremia has been reported in > 50% of hospitalized patients with AIDS. Among the many potential contributing factors are

• Administration of hypotonic fluids

• Impaired renal function

• Nonosmotic ADH release due to intravascular volume depletion

• Administration of drugs that impair renal water excretion

In addition, adrenal insufficiency has become increasingly common among AIDS patients as the result of cytomegalovirus adrenalitis, mycobacterial infection, or interference with adrenal glucocorticoid and mineralocorticoid synthesis by ketoconazole. SIADH may be present because of coexistent pulmonary or CNS infections.

Sidebar 97-1 Syndrome of Inappropriate ADH Secretion

The syndrome of inappropriate ADH secretion (SIADH) is attributed to excessive ADH release. It is defined as less-than-maximally-dilute urine in the presence of plasma hypo-osmolality (hyponatremia) without volume depletion or overload, emotional stress, pain, diuretics, or other drugs that stimulate ADH secretion in patients with normal cardiac, hepatic, renal, adrenal, and thyroid function. SIADH is associated with myriad disorders (see Table 97-5).

Symptoms and Signs

Symptoms mainly involve CNS dysfunction. However, when hyponatremia is accompanied by disturbances in total body Na content, signs of ECF volume depletion or overload also occur (see p. 823). In general, older chronically ill patients with hyponatremia develop more symptoms than younger otherwise healthy patients. Symptoms are also more severe with faster-onset hyponatremia. Symptoms generally occur when the effective plasma osmolality falls to < 240 mOsm/kg. Symptoms can be subtle and consist mainly of changes in mental status, including altered personality, lethargy, and confusion. As the serum Na falls to < 115 mEq/L, stupor, neuromuscular hyperexcitability, hyperreflexia, seizures, coma, and death can result.

Severe cerebral edema may occur in premenopausal women with acute hyponatremia, perhaps because

estrogen and progesterone inhibit brain Na^+, K^+-ATPase and decrease solute extrusion from brain cells. Sequelae include hypothalamic and posterior pituitary infarction and occasionally brain stem herniation.

Diagnosis

• Serum and urine electrolytes and osmolality

• Clinical assessment of volume status

Hyponatremia is occasionally suspected in patients who have neurologic abnormalities and are at risk. However, because findings are nonspecific, hyponatremia is often recognized only after serum electrolyte measurement.

[**Table 97-5.** Disorders Associated with Syndrome of Inappropriate ADH Secretion]

Serum Na may be low when severe hyperglycemia increases osmolality and water moves out of cells into the ECF. Serum Na concentration falls about 1.6 mEq/L for every 100-mg/dL (5.55-mmol/L) rise in the serum glucose concentration above normal. This condition is often called translocational hyponatremia because it is caused by translocation of Na across cell membranes. Pseudohyponatremia with normal serum osmolality may occur in hyperlipidemia or extreme hyperproteinemia, because the lipid or protein occupies space in the volume of serum taken for analysis; the concentration of Na in serum itself is not affected. Newer methods of measuring serum electrolytes with ion-selective electrodes circumvent this problem.

Identification of the cause: Identifying the cause can be complex. The history sometimes suggests a cause (eg, significant fluid loss due to vomiting or diarrhea, renal disease, compulsive fluid ingestion, intake of drugs that stimulate ADH release or enhance ADH action).

The volume status, particularly the presence of obvious volume depletion or overload, suggests certain causes (see Table 97-1). Overtly hypovolemic patients usually have an obvious source of fluid loss (typically treated with hypotonic fluid replacement). Overtly hypervolemic patients usually have a readily recognizable condition, such as heart failure or hepatic or renal disease. Euvolemic patients and patients with equivocal volume status require more laboratory testing to identify a cause.

Laboratory tests should include serum and urine osmolality and electrolytes. Euvolemic patients should also have thyroid and adrenal function tested. Hypo-osmolality in euvolemic patients should cause excretion of a large volume of dilute urine (eg, osmolality < 100 mOsm/kg and sp gr < 1.003). Serum Na concentration and serum osmolality that are low and urine osmolality that is inappropriately high (120 to 150 mmol/L) with respect to the low serum osmolality suggest volume overload, volume contraction, or SIADH. Volume overload and volume contraction are differentiated clinically (see pp. 822 and 823). When neither volume overload nor volume contraction appears likely, SIADH is considered. Patients with SIADH are usually euvolemic or slightly hypervolemic. BUN and creatinine values are normal, and serum uric acid is generally low. Urine Na concentration is usually > 30 mmol/L, and fractional excretion of Na is > 1% (for calculation, see p. 2310).

In patients with hypovolemia and normal renal function, Na reabsorption results in a urine Na of < 20 mmol/L. Urine Na > 20 mmol/L in hypovolemic patients suggests mineralocorticoid deficiency or salt-losing nephropathy. Hyperkalemia suggests adrenal insufficiency.

Treatment

• When hypovolemic, 0.9% saline

• When hypervolemic, fluid restriction and sometimes a diuretic

• When euvolemic, treatment of cause

• Rarely cautious correction with hypertonic (3%) saline

Rapid correction of hyponatremia, even mild hyponatremia, risks neurologic complications (see p. 828). Except possibly in the first few hours of treatment of severe hyponatremia, Na should be corrected no faster than 0.5 mEq/L/h. Even with severe hyponatremia, increase in serum Na concentration should not exceed 10 mEq/L over the first 24 h. Any identified cause of hyponatremia is treated concurrently.

Mild hyponatremia: Mild, asymptomatic hyponatremia (ie, serum Na > 120 mEq/L) requires restraint because small adjustments are generally sufficient. In diuretic-induced hyponatremia, elimination of the diuretic may be enough; some patients need some Na or K replacement. Similarly, when mild hyponatremia results from inappropriate hypotonic parenteral fluid administration in patients with impaired water excretion, merely altering fluid therapy may suffice.

With **hypovolemia** and normal adrenal function, administration of 0.9% saline usually corrects both hyponatremia and hypovolemia. When the serum Na is < 120 mEq/L, hyponatremia may not completely correct upon restoration of intravascular volume; restriction of free water ingestion to ≤ 500 to 1000 mL/24 h may be needed.

In **hypervolemic patients**, in whom hyponatremia is due to renal Na retention (eg, heart failure, cirrhosis, nephrotic syndrome) and dilution, water restriction combined with treatment of the underlying disorder is required. In patients with heart failure, an ACE inhibitor, in conjunction with a loop diuretic, can correct refractory hyponatremia. In other patients in whom simple fluid restriction is ineffective, a loop diuretic in escalating doses can be used, sometimes in conjunction with IV 0.9% normal saline. K and other electrolytes lost in the urine must be replaced. When hyponatremia is more severe and unresponsive to diuretics, intermittent or continuous hemofiltration may be needed to control ECF volume while hyponatremia is corrected with IV 0.9% normal saline.

In **euvolemia,** treatment is directed at the cause (eg, hypothyroidism, adrenal insufficiency, diuretic use). When SIADH is present, severe water restriction (eg, 250 to 500 mL/24 h) is generally required. Additionally, a loop diuretic may be combined with IV 0.9% saline as in hypervolemic hyponatremia. Lasting correction depends on successful treatment of the underlying disorder. When the underlying disorder is not correctable, as in metastatic cancer, and patients find severe water restriction unacceptable, demeclocycline (300 to 600 mg q 12 h) may be helpful by inducing a concentrating defect in the kidneys. However, demeclocycline may cause acute renal failure. Renal failure is usually reversible when the drug is stopped. IV conivaptan, an ADH receptor antagonist, causes effective water diuresis without significant loss of electrolytes in the urine and can be used in hospitalized patients for treatment of resistant hyponatremia.

Severe hyponatremia: Severe hyponatremia (serum Na < 109 mEq/L; effective osmolality < 238 mOsm/kg) in asymptomatic patients can be treated safely with stringent restriction of water intake. Treatment is more controversial when neurologic symptoms (eg, confusion, lethargy, seizures, coma) are present. The debate primarily concerns the pace and degree of hyponatremia correction. Many experts recommend that serum Na be raised no faster than 1 mEq/L/h, but replacement rates of up to 2 mEq/L/h for the first 2 to 3 h have been suggested for patients with seizures. Regardless, the rise should be ≤ 10 mEq/L over the first 24 h. More vigorous correction risks precipitation of osmotic demyelination syndrome.

Hypertonic (3%) saline (containing 513 mEq Na/L) may be used, but only with frequent (q 2 to 4 h) electrolyte determinations. For patients with seizures or coma, ≤ 100 mL/h may be administered over 4 to 6 h in amounts sufficient to raise the serum Na 4 to 6 mEq/L. This amount (in mEq) may be calculated using the Na deficit formula as

(Desired change in Na) × TBW

where TBW is 0.6 × body weight in kg in men and 0.5 × body weight in kg in women.

For example, the amount of Na needed to raise the Na from 106 to 112 in a 70-kg man can be calculated as follows:

(112 mEq/L - 106 mEq/L) × (0.6 L/kg × 70 kg) = 252 mEq

Because there is 513 mEq Na/L in hypertonic saline, roughly 0.5 L of hypertonic saline is needed to raise the Na from 106 to 112 mEq/L.

Adjustments may be needed based on serum Na concentrations, which are monitored closely for the first few hours of treatment. Patients with seizures, coma, or altered mental status need supportive treatment, which may involve endotracheal intubation, mechanical ventilation, and benzodiazepines (eg, lorazepam 1 to 2 mg IV q 5 to 10 min prn) for seizures.

Osmotic demyelination syndrome: Osmotic demyelination syndrome (previously called central pontine myelinolysis) may follow too-rapid correction of hyponatremia. Demyelination may affect the pons and other areas of the brain. Lesions are more common among patients with alcoholism, undernutrition, or other chronic debilitating illness. Flaccid paralysis, dysarthria, and dysphagia can evolve over a few days or weeks. The lesion may extend dorsally to involve sensory tracts and leave patients with a locked-in syndrome (an awake and sentient state in which patients, because of generalized motor paralysis, cannot communicate, except possibly by coded eye movements). Damage often is permanent. When Na is replaced too rapidly (eg, > 14 mEq/L/8 h) and neurologic symptoms start to develop, it is critical to prevent further serum Na increases by stopping hypertonic fluids. In such cases, inducing hyponatremia with hypotonic fluid may mitigate the development of permanent neurologic damage.

Hypernatremia

(For hypernatremia in neonates, see p. 2797.)

Hypernatremia is serum Na concentration > 145 mEq/L. It implies a deficit of total body water relative to total body Na, caused by water intake being less than water losses. A major symptom is thirst; other clinical manifestations are primarily neurologic (due to an osmotic shift of water out of brain cells), including confusion, neuromuscular excitability, seizures, and coma. Diagnosis requires measurement of serum Na and sometimes other tests. Treatment is usually controlled water replacement. When the response is poor, testing (eg, monitored water deprivation or administration of vasopressin) is directed at detecting causes other than decreased water intake.

Etiology

Hypernatremia reflects a deficit of total body water (TBW) relative to total body Na content. Because total body Na content is reflected by ECF volume status, hypernatremia must be considered along with status of the ECF volume: hypovolemia, euvolemia, and hypervolemia. Note that the ECF volume is not the same as effective plasma volume. For example, decreased effective plasma volume may occur with decreased ECF volume, but it may also occur with an increased ECF volume (eg, in heart failure, hypoalbuminemia, or capillary leak syndrome).

Hypernatremia usually implies either an impaired thirst mechanism or limited access to water. The severity of the underlying disorder that results in an inability to drink in response to thirst and the effects of brain hyperosmolality are thought to be responsible for a high mortality rate in hospitalized adults with hypernatremia. There are several common causes of hypernatremia (see Table 97-6).

Hypovolemic hypernatremia: Hypernatremia associated with hypovolemia occurs with Na loss accompanied by a relatively greater loss of water from the body. Common extrarenal causes include most of those that cause hyponatremia and volume depletion (see p. 823). Either hypernatremia or hyponatremia can occur with severe volume loss, depending on the relative amounts of Na and water lost and the amount of water ingested before presentation.

Renal causes of hypernatremia and volume depletion include therapy with diuretics. Loop diuretics inhibit Na reabsorption in the concentrating portion of the nephrons and can increase water clearance. Osmotic diuresis can also impair renal concentrating capacity because of a hypertonic substance present in the tubular lumen of the distal nephron. Glycerol, mannitol, and occasionally urea can cause osmotic diuresis

resulting in hypernatremia. The most common cause of hypernatremia due to osmotic diuresis is hyperglycemia in patients with diabetes. Because glucose does not penetrate cells in the absence of insulin, hyperglycemia further dehydrates the ICF compartment. The degree of hyperosmolality in hyperglycemia may be obscured by the lowering of serum Na resulting from movement of water out of cells into the ECF (translational hyponatremia—see Hyponatremia on p. 823). Patients with renal disease can also be predisposed to hypernatremia when their kidneys are unable to maximally concentrate urine.

Euvolemic hypernatremia: Hypernatremia with euvolemia is a decrease in TBW with nearnormal total body Na (pure water deficit). Extrarenal causes of water loss, such as excessive sweating, result in some Na loss, but because sweat is hypotonic, hypernatremia can result before significant hypovolemia. A deficit of almost purely water also occurs in central and nephrogenic diabetes insipidus.

Essential hypernatremia (primary hypodipsia) occasionally occurs in children with brain damage and in chronically ill elderly adults. It is characterized by an impaired thirst mechanism (eg, caused by lesions of the brain's thirst center). Altered osmotic trigger for ADH release is another possible cause of euvolemic hypernatremia; some lesions cause both an impaired thirst mechanism and an altered osmotic trigger. The nonosmotic release of ADH seems intact, and these patients are generally euvolemic.

Hypervolemic hypernatremia: Hypernatremia in rare cases is associated with volume overload. In this case, hypernatremia results from a grossly elevated Na intake associated with limited access to water. One example is the excessive administration of hypertonic $NaHCO_3$ during treatment of lactic acidosis. Hypernatremia can also be caused by the administration of hypertonic saline or incorrectly formulated hyperalimentation.

Hypernatremia in the elderly: Hypernatremia is common among the elderly, particularly postoperative patients and those receiving tube feedings or parenteral nutrition. Other contributing factors may include the following:

[**Table 97-6.** Principal Causes of Hypernatremia]

- Dependence on others to obtain water
- Impaired thirst mechanism
- Impaired renal concentrating capacity (due to diuretics, impaired ADH release, or nephron loss accompanying aging or other renal disease)
- Impaired angiotensin II production (which may contribute directly to the impaired thirst mechanism)

Symptoms and Signs

The major symptom of hypernatremia is thirst. The absence of thirst in conscious patients with hypernatremia suggests an impaired thirst mechanism. Patients with difficulty communicating may be unable to express thirst or obtain access to water.

The major signs of hypernatremia result from CNS dysfunction due to brain cell shrinkage. Confusion, neuromuscular excitability, hyperreflexia, seizures, or coma may result; cerebrovascular damage with subcortical or subarachnoid hemorrhage and venous thromboses are common among patients who died from severe hypernatremia.

In chronic hypernatremia, osmotically active substances occur in CNS cells (idiogenic osmoles) and increase intracellular osmolality. Therefore, the degree of brain cell dehydration and resultant CNS symptoms are less severe in chronic than in acute hypernatremia.

When hypernatremia occurs with abnormal total body Na, the typical symptoms of volume depletion or overload are present (see Volume Depletion on p. 822 and Volume Overload on p. 823). A large volume of hypotonic urine is characteristically excreted in patients with renal concentrating defects. When losses are extrarenal, the route of water loss is often evident (eg, vomiting, diarrhea, excessive sweating), and

the urinary Na concentration is low.

Diagnosis

• Serum Na

The diagnosis is clinical and by measuring serum Na. In patients who do not respond to simple rehydration or in whom hypernatremia recurs despite adequate access to water, further diagnostic testing is warranted. Determination of the underlying disorder requires assessment of urine volume and osmolality, particularly after water deprivation.

In patients with increased urine output, a water deprivation test (see p. 773) is occasionally used to differentiate among several polyuric states, such as central and nephrogenic diabetes insipidus.

Treatment

• Replacement of intravascular volume and of free water

Replacement of intravascular volume and of free water is the main goal of treatment. Oral hydration is effective in conscious patients without significant GI dysfunction. In severe hypernatremia or in patients unable to drink because of continued vomiting or mental status changes, IV hydration is preferred. Hypernatremia that lasts < 24 h should be corrected within 24 h. However, hypernatremia that is chronic or of unknown duration should be corrected over 48 h, and the serum osmolality should be lowered at a rate of no faster than 2 mOsm/L/h to avoid cerebral edema caused by excess brain solute. The amount of water (in liters) necessary to replace existing deficits may be estimated by the following formula:

$$\text{Free water deficit} = \text{TBW} \times [\text{serum Na}/140) - 1]$$

where TBW is in liters and is estimated by multiplying weight in kilograms by 0.6; serum Na is in mEq/L. This formula assumes constant total body Na content. In patients with hypernatremia and depletion of total body Na content (ie, who have volume depletion), the free water deficit is greater than that estimated by the formula.

In patients with hypernatremia and ECF volume overload (excess total body Na content), the free water deficit can be replaced with 5% D/W, which can be supplemented with a loop diuretic. However, too-rapid infusion of 5% D/W may cause glycosuria, thereby increasing salt-free water excretion and hypertonicity, especially in patients with diabetes mellitus. Other electrolytes, including serum K, should be monitored and should be replaced as needed.

In patients with hypernatremia and euvolemia, free water can be replaced using either 5% D/W or 0.45% saline.

Treatment of patients with central diabetes insipidus is discussed on p. 774. Acquired nephrogenic diabetes insipidus is discussed on p. 2424.

In patients with hypernatremia and hypovolemia, particularly in patients with diabetes with nonketotic hyperglycemic coma, 0.45% saline can be given as an alternative to a combination of 0.9% normal saline and 5% D/W to replenish Na and free water. Alternatively, ECF volume and free water can be replaced separately, using the formula given previously to estimate the free water deficit. When severe acidosis (pH < 7.10) is present, $NaHCO_3$ solution can be added to 5% D/W or 0.45% saline, as long as the final solution remains hypotonic.

Disorders of Potassium Concentration

K is the most abundant intracellular cation, but only about 2% of total body K is extracellular. Because most intracellular K is contained within muscle cells, total body K is roughly proportional to lean body mass. An average 70-kg adult has about 3500 mEq of K.

K is a major determinant of intracellular osmolality. The ratio between ICF and ECF K concentrations

strongly influences cell membrane polarization, which in turn influences important cell processes, such as the conduction of nerve impulses and muscle (including myocardial) cell contraction. Thus, relatively small alterations in serum K concentration can have significant clinical manifestations.

In the absence of factors that shift K in or out of cells (see p. 832), the serum K concentration correlates closely with total body K content. Once intracellular and extracellular concentrations are stable, a decrease in serum K concentration of about 1 mEq/L indicates a total K deficit of about 200 to 400 mEq. Patients with K < 3 mEq/L typically have a significant K deficit.

K shifts: Factors that shift K in or out of cells include the following:

• Insulin concentrations

• β-Adrenergic activity

• Acid-base status

Insulin moves K into cells; high concentrations of insulin thus lower serum K concentration. Low insulin concentrations, as in diabetic ketoacidosis, cause K to move out of cells, thus raising serum K, sometimes even in the presence of total body K deficiency.

β-Adrenergic agonists, especially selective β_2-agonists, move K into cells, whereas β-blockade and α-agonists promote movement of K out of cells.

Acute metabolic acidosis causes K to move out of cells, whereas acute metabolic alkalosis causes K to move into cells. However, changes in serum HCO_3 concentration may be more important than changes in pH; acidosis caused by accumulation of mineral acids (nonanion gap, hyperchloremic acidosis) is more likely to elevate serum K. In contrast, metabolic acidosis due to accumulation of organic acids (increased anion gap acidosis) is not associated with hyperkalemia. Thus, the hyperkalemia common in diabetic ketoacidosis results more from insulin deficiency than from acidosis. Acute respiratory acidosis and alkalosis affect serum K concentration less than metabolic acidosis and alkalosis. Nonetheless, serum K concentration should always be interpreted in the context of the serum pH (and HCO_3 concentration).

K metabolism: Dietary K intake normally varies between 40 and 150 mEq/day. In the steady state, fecal losses are usually close to 10% of intake. Urinary excretion contributes to K balance.

When K intake is > 150 mEq/day, about 50% of the excess K appears in the urine over the next several hours. Most of the remainder is transferred into the intracellular compartment, thus minimizing the rise in serum K. When elevated K intake continues, aldosterone secretion is stimulated and thus renal K excretion rises. In addition, K absorption from stool appears to be under some regulation and may fall by 50% in chronic K excess.

When K intake falls, intracellular K again serves to buffer wide swings in serum K concentration. Renal K conservation develops relatively slowly in response to decreases in dietary K and is far less efficient than the kidneys' ability to conserve Na. Thus, K depletion is a frequent clinical problem. Urinary K excretion of 10 mEq/day represents near-maximal renal K conservation and implies significant K depletion.

Acute acidosis impairs K excretion, whereas chronic acidosis and acute alkalosis can promote K excretion. Increased delivery of Na to the distal nephrons, as occurs with high Na intake or loop diuretic therapy, promotes K excretion.

False K concentrations: Pseudohypokalemia, or falsely low serum K, occasionally occurs in patients with chronic myelocytic leukemia with a WBC count > $10^5/\mu L$ when the specimen remains at room temperature before being processed because of uptake of serum K by abnormal leukocytes in the sample. It is prevented by prompt separation of plasma or serum in blood samples.

Pseudohyperkalemia, or falsely elevated serum K, is more common, typically occurring due to hemolysis

and release of intracellular K. To prevent false results, phlebotomy personnel should not rapidly aspirate blood through a narrow-gauge needle or excessively agitate blood samples. Pseudohyperkalemia can also result from platelet count > 400,000/µL due to release of K from platelets during clotting. In cases of pseudohyperkalemia, the plasma K (unclotted blood), as opposed to serum K, is normal.

Hypokalemia

Hypokalemia is serum K concentration < 3.5 mEq/L caused by a deficit in total body K stores or abnormal movement of K into cells. The most common causes are excess losses from the kidneys or GI tract. Clinical features include muscle weakness and polyuria; cardiac hyperexcitability may occur with severe hypokalemia. Diagnosis is by serum measurement. Treatment is giving K and managing the cause.

Etiology

Hypokalemia can be caused by decreased intake of K but is usually caused by excessive losses of K in the urine or from the GI tract.

GI tract losses: Abnormal GI K losses occur in all of the following:

- Chronic diarrhea, including chronic laxative abuse and bowel diversion
- Clay (bentonite) ingestion, which binds K and greatly decreases absorption
- Vomiting
- Protracted gastric suction (which removes volume and HCl, causing the kidneys to excrete HCO_3 and, to electrically balance lost HCO_3, K)
- Rarely, villous adenoma of the colon, which causes massive K secretion

GI K losses may be compounded by concomitant renal K losses due to metabolic alkalosis and stimulation of aldosterone due to volume depletion.

Intracellular shift: The transcellular shift of K into cells may also cause hypokalemia. This shift can occur in any of the following:

- Glycogenesis during TPN or enteral hyperalimentation (stimulating insulin release)
- After administration of insulin
- Stimulation of the sympathetic nervous system, particularly with β_2-agonists (eg, albuterol, terbutaline), which may increase cellular K uptake
- Thyrotoxicosis (occasionally) due to excessive β-sympathetic stimulation (hypokalemic thyrotoxic periodic paralysis)
- Familial periodic paralysis (see p. 3008), a rare autosomal dominant disorder characterized by transient episodes of profound hypokalemia thought to be due to sudden abnormal shifts of K into cells. Episodes frequently involve varying degrees of paralysis. They are typically precipitated by a large carbohydrate meal or strenuous exercise.

Renal losses: Various disorders can increase renal K excretion. Excess mineralocorticoid effect can directly increase K secretion by the distal nephrons and occurs in any of the following:

- Adrenal steroid excess that is due to Cushing's syndrome, primary hyperaldosteronism, rare renin-secreting tumors, glucocorticoid-remediable aldosteronism (a rare inherited disorder involving abnormal

aldosterone metabolism), and congenital adrenal hyperplasia.

- Ingestion of substances such as glycyrrhizin (present in natural licorice and used in the manufacture of chewing tobacco), which inhibits the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSDH), preventing the conversion of cortisol, which has some mineralocorticoid activity, to cortisone, which does not, resulting in high circulating concentrations of cortisol and renal K wasting.

- Bartter and Gitelman's syndromes, uncommon genetic disorders characterized by renal K and Na wasting, excessive production of renin and aldosterone, and normotension. Bartter syndrome (see also p. 2988) is caused by mutations in a loop diuretic-sensitive ion transport mechanism in the loop of Henle. Gitelman's syndrome is caused by loss of function mutations in a thiazide-sensitive ion transport mechanism in the distal nephron.

Liddle syndrome (see also p. 2423) is a rare autosomal dominant disorder characterized by severe hypertension and hypokalemia. Liddle syndrome is caused by unrestrained Na reabsorption in the distal nephron due to one of several mutations found in genes encoding for epithelial Na channel subunits. Inappropriately high reabsorption of Na results in both hypertension and renal K wasting.

Renal K wasting can also be caused by numerous congenital and acquired renal tubular diseases, such as the renal tubular acidoses and Fanconi syndrome, an unusual syndrome resulting in renal wasting of K, glucose, phosphate, uric acid, and amino acids.

Hypomagnesemia is a common correlate of hypokalemia. Much of this is attributable to common underlying causes (ie, diuretics, diarrhea), but hypomagnesemia itself may also result in increased renal K losses.

Drugs: Diuretics are by far the most commonly used drugs that cause hypokalemia. K-wasting diuretics that block Na reabsorption proximal to the distal nephron include

- Thiazides

- Loop diuretics

- Osmotic diuretics

By inducing diarrhea, laxatives, especially when abused, can cause hypokalemia. Surreptitious diuretic or laxative abuse or both is a frequent cause of persistent hypokalemia, particularly among patients preoccupied with weight loss and among health care practitioners with access to prescription drugs.

Other drugs that can cause hypokalemia include

- Amphotericin B

- Antipseudomonal penicillins (eg, carbenicillin)

- Penicillin in high doses

- Theophylline intoxication (both acute and chronic)

Symptoms and Signs

Mild hypokalemia (serum K 3 to 3.5 mEq/L) rarely causes symptoms. Serum K < 3 mEq/L generally causes muscle weakness and may lead to paralysis and respiratory failure. Other muscular dysfunction includes cramping, fasciculations, paralytic ileus, hypoventilation, hypotension, tetany, and rhabdomyolysis. Persistent hypokalemia can impair renal concentrating ability, causing polyuria with secondary polydipsia.

Diagnosis

• Serum K measurement

• ECG

• When the mechanism not evident clinically, 24-h urinary K excretion and serum Mg concentration

Hypokalemia (serum K < 3.5 mEq/L) may be found on routine serum electrolyte measurement. It should be suspected in patients with typical changes on an ECG or who have muscular symptoms and risk factors and confirmed by blood testing.

ECG: ECG should be done on patients with hypokalemia. Cardiac effects of hypokalemia are usually minimal until serum K concentrations are < 3 mEq/L. Hypokalemia causes sagging of the ST segment, depression of the T wave, and elevation of the U wave. With marked hypokalemia, the T wave becomes progressively smaller and the U wave becomes increasingly larger. Sometimes, a flat or positive T wave merges with a positive U wave, which may be confused with QT prolongation (see Fig. 97-2). Hypokalemia may cause premature ventricular and atrial contractions, ventricular and atrial tachyarrhythmias, and 2nd- or 3rd-degree atrioventricular block. Such arrhythmias become more severe with increasingly severe hypokalemia; eventually, ventricular fibrillation may occur. Patients with significant preexisting heart disease and patients receiving digoxin are at risk of cardiac conduction abnormalities even from mild hypokalemia.

Diagnosis of cause: The cause is usually apparent by history (particularly the drug history); when it is not, further investigation is warranted. After acidosis and other causes of intracellular K shift (increased β-adrenergic effect, hyperinsulinemia) have been eliminated, 24-h urinary K and serum Mg concentrations are measured. In hypokalemia, K secretion is normally < 15 mEq/L. Extrarenal (GI) K loss or decreased K ingestion is suspected in chronic unexplained hypokalemia when renal K secretion is < 15 mEq/L. Secretion of > 15 mEq/L suggests a renal cause for K loss. Unexplained hypokalemia with increased renal K secretion and hypertension suggests an aldosterone-secreting tumor or Liddle syndrome. Unexplained hypokalemia with increased renal K loss and normal BP suggests Bartter or Gitelman's syndrome, but hypomagnesemia, surreptitious vomiting, and diuretic abuse are more common and should also be considered.

Treatment

• Oral K supplements

• IV K supplements for severe hyperkalemia or ongoing K losses

Many oral K supplements are available. Because high single doses can cause GI irritation and occasional bleeding, deficits are usually replaced in divided doses. Liquid KCl given orally elevates concentrations within 1 to 2 h but has a bitter taste and is tolerated particularly poorly in doses > 25 to 50 mEq. Wax-impregnated KCl preparations are safe and better tolerated. GI bleeding may be even less common with microencapsulated KCl preparations. Several of these preparations contain 8 or 10 mEq/capsule. Because a decrease in serum K of 1 mEq/L correlates with about a 200- to 400-mEq deficit in total body K stores, total deficit can be estimated and replaced over a number of days at 20 to 80 mEq/day.

When hypokalemia is severe (eg, with ECG changes or severe symptoms), is unresponsive

[**Fig. 97-2.** ECG patterns in hypokalemia and hyperkalemia.]

to oral therapy, or occurs in hospitalized patients who are taking digitalis or who have significant heart disease or ongoing losses, K must be replaced IV. Because K solutions can irritate peripheral veins, the concentration should not exceed 40 mEq/L. The rate of correction of hypokalemia is limited because of the lag in K movement into cells. *Routine infusion rates should not exceed 10 mEq/h.* In hypokalemic-induced arrhythmia, IV KCl must be given more rapidly, usually through a central vein or using multiple peripheral veins simultaneously. Infusion of 40 mEq KCl/h can be undertaken but only with continuous cardiac monitoring and hourly serum K determinations. Glucose solutions are avoided because elevation

in the serum insulin concentrations could result in transient worsening of hypokalemia.

Even when K deficits are severe, it is rarely necessary to give > 100 to 120 mEq of K in a 24-h period unless K loss continues. In K deficit with high serum K concentration, as in diabetic ketoacidosis, IV K is deferred until the serum K starts to fall. When hypokalemia occurs with hypomagnesemia, both the K and Mg deficiencies must be corrected to stop ongoing renal K wasting (see Hypomagnesemia on p. 852).

Prevention

Routine K replacement is not necessary in most patients receiving diuretics. However, serum K should be monitored during diuretic use when risk of hyperkalemia or of its complications is high. Risk is high in

- Patients with decreased left ventricular function
- Patients taking digoxin
- Patients with diabetes (in whom insulin concentrations can fluctuate)
- Patients with asthma who are taking β_2-agonists

Triamterene 100 mg po once/day or spironolactone 25 mg po qid does not increase K excretion and may be useful in patients who become hypokalemic but must use diuretics. When hypokalemia develops, K supplementation, usually with oral KCl, is indicated.

Hyperkalemia

Hyperkalemia is serum K concentration > 5.5 mEq/L resulting from excess total body K stores or abnormal movement of K out of cells. There are usually several simultaneous contributing factors, including increased K intake, drugs that impair renal K excretion, and acute or chronic kidney disease. It can also occur in metabolic acidosis as in diabetic ketoacidosis. Clinical manifestations are generally neuromuscular, resulting in muscle weakness and cardiac toxicity that, when severe, can degenerate to ventricular fibrillation or asystole. Diagnosis is by measuring serum K. Treatment may involve decreasing K intake, adjusting drugs, giving a cation exchange resin and, in emergencies, Ca gluconate, insulin, and dialysis.

Etiology

The most common cause of increased serum K concentration is probably pseudohyperkalemia caused by hemolysis of RBCs in the blood sample. Normal kidneys eventually excrete K loads, so sustained, nonartifactual hyperkalemia usually implies diminished renal K excretion. However, other factors usually contribute. They can include increased K intake, increased K release from cells, or both (see Table 97-7). When sufficient KCl is ingested or given parenterally, severe hyperkalemia may result even with normal renal function but is usually temporary.

Hyperkalemia due to total body K excess is particularly common in oliguric states (especially acute renal failure) and with rhabdomyolysis, burns, bleeding into soft tissue or the GI tract, and adrenal insufficiency. In chronic renal failure, hyperkalemia is uncommon until the GFR falls to < 10 to 15 mL/min unless dietary or IV K intake is excessive.

Symptoms and Signs

Although flaccid paralysis occasionally occurs, hyperkalemia is usually asymptomatic until cardiac toxicity develops.

In the rare disorder hyperkalemic familial periodic paralysis, weakness frequently develops during attacks and can progress to frank paralysis.

Diagnosis

• Serum K measurement

• ECG

• Review of drug use

• Assessment of renal function

Hyperkalemia (serum K > 5.5 mEq/L) may be found on routine serum electrolyte measurement. It should be suspected in patients with typical changes on an ECG or patients at high risk, such as those with renal failure, advanced heart failure treated with ACE inhibitors and K-sparing diuretics, or urinary obstruction.

ECG: ECG should be done on patients with hyperkalemia. ECG changes (see Fig. 97-2) are frequently visible when serum K is > 5.5 mEq/L. Slowing of conduction characterized by an increased PR interval and shortening of the QT interval as well as tall, symmetric, peaked T

[**Table 97-7.** Factors Contributing to Hyperkalemia]

waves are visible initially. K > 6.5 mEq/L causes further slowing of conduction with widening of the QRS interval, disappearance of the P wave, and nodal and escape ventricular arrhythmias. Finally, the QRS complex degenerates into a sine wave pattern, and ventricular fibrillation or asystole ensues.

Diagnosis of the cause: Pseudohyperkalemia should be considered in patients without risk factors or ECG abnormalities. Hemolysis may be reported by the laboratory. When pseudohyperkalemia is suspected, K concentration should be repeated, taking measures to avoid hemolysis of the sample.

Diagnosis of the cause of hyperkalemia requires a detailed history, including a review of drugs, a physical examination with emphasis on volume status, and measurement of electrolytes, BUN, and creatinine. In cases in which renal failure is present, additional tests, including renal ultrasonography to exclude obstruction, are needed (see p. 2438).

Treatment

• Treatment of the cause

• For mild hyperkalemia, Na polystyrene sulfonate

For moderate or severe hyperkalemia, IV insulin and glucose, an IV Ca solution, possibly an inhaled β_2-agonist, and usually hemodialysis

Mild hyperkalemia: Patients with serum K < 6 mEq/L and no ECG abnormalities may respond to diminished K intake or stopping K-elevating drugs. The addition of a loop diuretic enhances renal K excretion as long as volume depletion is not present.

Na polystyrene sulfonate in sorbitol can be given (15 to 30 g in 30 to 70 mL of 70% sorbitol po q 4 to 6 h). It acts as a cation exchange resin and removes K through the GI mucosa. Sorbitol is administered with the resin to ensure passage through the GI tract. Patients unable to take drugs orally because of nausea or other reasons may be given similar doses by enema. Enemas are not as effective at lowering K in patients with ileus. Enemas should not be used if acute abdomen is suspected. About 1 mEq of K is removed per gram of resin given. Resin therapy is slow and often fails to lower serum K significantly in hypercatabolic states. Because Na is exchanged for K when Na polystyrene sulfonate is used, Na overload may occur, particularly in oliguric patients with preexisting volume overload.

Moderate to severe hyperkalemia: Serum K between 6 and 6.5 mEq/L needs prompt attention, but the actual treatment depends on the clinical situation. If no ECG changes are present and renal function is intact, maneuvers described previously are usually effective. Follow-up serum K levels are needed to ensure that the hyperkalemia has been successfully treated. If serum K is > 6.5 mEq/L, more aggressive

therapy is required. Administration of regular insulin 5 to 10 units IV is followed immediately by or administered simultaneously with rapid infusion of 50 mL 50% glucose. Infusion of 10% D/W should follow at 50 mL/h to prevent hypoglycemia. The effect on serum K peaks in 1 h and lasts for several hours.

If ECG changes include the loss of P-wave or widening of the QRS complex, treatment with IV Ca as well as insulin and glucose is indicated; 10 to 20 mL 10% Ca gluconate (or 5 to 10 mL 22% Ca gluceptate) is given IV over 5 to 10 min. Ca antagonizes the effect of hyperkalemia on cardiac muscle. Ca should be given with caution to patients taking digoxin because of the risk of precipitating hypokalemia-related arrhythmias. If the ECG shows a sine wave pattern or asystole, Ca gluconate may be given more rapidly (5 to 10 mL IV over 2 min). CaCl can also be used but can be irritating to peripheral veins and cause tissue necrosis if extravasated. CaCl should be given only through a correctly positioned central venous catheter. The benefits of Ca occur within minutes but last only 20 to 30 min. Ca infusion is a temporizing measure while awaiting the effects of other treatments or initiation of hemodialysis and may need to be repeated.

A high-dose β_2-agonist, such as albuterol 10 to 20 mg inhaled over 10 min (5 mg/mL concentration), can lower serum K by 0.5 to 1.5 mEq/L and may be a helpful adjunct. The peak effect occurs in 90 min. However, β_2-agonists are contraindicated in patients with unstable angina and acute MI.

Administration of IV $NaHCO_3$ is controversial. It may lower serum K over several hours. Reduction may result from alkalinization or the hypertonicity due to the concentrated Na in the preparation. The hypertonic Na that it contains may be harmful for dialysis patients who also may have volume overload. When given, the usual dose is 45 mEq (1 ampule of 7.5% $NaHCO_3$) infused over 5 min and repeated in 30 min. HCO_3 therapy has little effect when used by itself in patients with severe renal insufficiency unless acidemia is also present.

In addition to strategies for lowering K by shifting it into cells, maneuvers to remove K from the body should also be done early in the treatment of severe or symptomatic hyperkalemia. K can be removed via the GI tract by administration of Na polystyrene sulfonate (see p. 836) or by hemodialysis. Hemodialysis should be instituted promptly after emergency measures in patients with renal failure or when emergency treatment is ineffective. Dialysis should be considered early in patients with end-stage renal disease and hyperkalemia because they are at increased risk of progression to more severe hyperkalemia and serious cardiac arrhythmias. Peritoneal dialysis is relatively inefficient at removing K.

Disorders of Calcium Concentration

Ca is required for the proper functioning of muscle contraction, nerve conduction, hormone release, and blood coagulation. In addition, proper Ca concentration is required for various other metabolic processes.

Maintenance of body Ca stores depends on

- Dietary Ca intake
- Absorption of Ca from the GI tract
- Renal Ca excretion

In a balanced diet, roughly 1000 mg of Ca is ingested each day and about another 200 mg/day is secreted into the GI tract in the bile and other GI secretions. Depending on the concentration of circulating vitamin D, particularly $1,25(OH)_2D$ (1,25-dihydroxycholecalciferol, calcitriol, or active vitamin D, which is converted in the kidney from 25(OH)D, the inactive form), roughly 200 to 400 mg of Ca is absorbed from the intestine each day. The remaining 800 to 1000 mg appears in the stool. Ca balance is maintained through renal Ca excretion averaging 200 mg/day.

Both extracellular and intracellular Ca concentrations are tightly regulated by bidirectional Ca transport across the plasma membrane of cells and intracellular organelles, such as the endoplasmic reticulum, the

sarcoplasmic reticulum of muscle cells, and the mitochondria. Cytosolic ionized Ca is maintained within the micromolar range (< 1/1000 of the serum concentration). Ionized Ca acts as an intracellular 2nd messenger; it is involved in skeletal muscle contraction, excitation-contraction coupling in cardiac and smooth muscle, and activation of protein kinases and enzyme phosphorylation. Ca is also involved in the action of other intracellular messengers, such as cAMP and inositol 1,4,5-triphosphate, and thus mediates the cellular response to numerous hormones, including epinephrine, glucagon, ADH (vasopressin), secretin, and cholecystokinin. Parathyroid hormone (PTH) increases urinary cAMP.

Despite its important intracellular roles, about 99% of body Ca is in bone, mainly as hydroxyapatite crystals. About 1% of bone Ca is freely exchangeable with the ECF and, therefore, is available for buffering changes in Ca balance.

Normal total serum Ca concentration ranges from 8.8 to 10.4 mg/dL (2.20 to 2.60 mmol/L). About 40% of the total blood Ca is bound to plasma proteins, primarily albumin. The remaining 60% includes ionized Ca plus Ca complexed with phosphate (PO_4) and citrate. Total Ca (ie, protein-bound, complexed, and ionized Ca) is usually what is determined by clinical laboratory measurement. Ideally, ionized or free Ca should be determined because it is the physiologically active form of Ca in plasma; this determination, because of its technical difficulty, is usually restricted to patients in whom significant alteration of protein binding of serum Ca is suspected. Ionized Ca is generally assumed to be about 50% of the total serum Ca.

Regulation of Calcium Metabolism

The metabolism of Ca and of PO_4 (see p. 850) is intimately related. The regulation of both Ca and PO_4 balance is greatly influenced by concentrations of circulating PTH, vitamin D, and, to a lesser extent, calcitonin. Ca and inorganic PO_4 concentrations are also linked by their ability to chemically react to form $CaPO_4$. The product of concentrations of Ca and PO_4 (in mEq/L) is estimated to be 60 normally; when the product exceeds 70, precipitation of $CaPO_4$ crystals in soft tissue is much more likely. Calcification of vascular tissue accelerates arteriosclerotic vascular disease and may occur when the Ca × PO_4 product is even lower (> 55), especially in patients with chronic kidney disease.

PTH is secreted by the parathyroid glands. It has several actions, but perhaps the most important is to defend against hypocalcemia. Parathyroid cells sense decreases in serum Ca and, in response, release preformed PTH into the circulation. PTH increases serum Ca within minutes by increasing renal and intestinal absorption of Ca and by rapidly mobilizing Ca and PO_4 from bone (bone resorption). Renal Ca excretion generally parallels Na excretion and is influenced by many of the same factors that govern Na transport in the proximal tubule. However, PTH enhances distal tubular Ca reabsorption independently of Na. PTH also decreases renal PO_4 reabsorption and thus increases renal PO_4 losses. Renal PO_4 loss prevents the solubility product of Ca and PO_4 from being exceeded in plasma as Ca concentrations rise in response to PTH. PTH also increases serum Ca by stimulating conversion of vitamin D (see p. 41) to its most active form, calcitriol. This form of vitamin D increases the percentage of dietary Ca absorbed by the intestine. Despite increased Ca absorption, long-term increases in PTH secretion generally result in further bone resorption by inhibiting osteoblastic function and promoting osteoclastic activity. PTH and vitamin D both function as important regulators of bone growth and bone remodeling (see p. 41).

Radioimmunoassays for the intact PTH molecule are still the recommended way to test for PTH. Second-generation assays for intact PTH are available. These tests measure bioavailable PTH or complete PTH. They give values equal to 50 to 60% of those obtained with the older assay. Usefulness of the newer assays is under investigation. Sometimes total or nephrogenous cAMP excretion is measured in diagnosis of pseudohypoparathyroidism.

Calcitonin is secreted by the thyroid parafollicular cells (C cells). Calcitonin tends to lower serum Ca concentration by enhancing cellular uptake, renal excretion, and bone formation. The effects of calcitonin on bone metabolism are much weaker than those of either PTH or vitamin D.

Hypocalcemia

(Hypocalcemia in neonates is discussed on p. 2794.)

Hypocalcemia is total serum Ca concentration < 8.8 mg/dL (< 2.20 mmol/L) in the presence of normal plasma protein concentrations or a serum ionized Ca concentration < 4.7 mg/dL (< 1.17 mmol/L). Causes include hypoparathyroidism, vitamin D deficiency, and renal disease. Manifestations include paresthesias, tetany, and, when severe, seizures, encephalopathy, and heart failure. Diagnosis involves measurement of serum Ca with adjustment for serum albumin concentration. Treatment is administration of Ca, sometimes with vitamin D.

Etiology

Hypocalcemia has a number of causes, including

• Hypoparathyroidism

• Pseudohypoparathyroidism

• Vitamin D deficiency and dependency

• Renal disease

Hypoparathyroidism: Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia and often causes chronic tetany. Hypoparathyroidism results from deficient parathyroid hormone (PTH), which can occur in autoimmune disorders or after the accidental removal of or damage to several parathyroid glands during thyroidectomy. Transient hypoparathyroidism is common after subtotal thyroidectomy, but permanent hypoparathyroidism occurs after < 3% of such thyroidectomies done by experienced surgeons. Manifestations of hypocalcemia usually begin about 24 to 48 h postoperatively but may occur after months or years. PTH deficiency is more common after radical thyroidectomy for cancer or as the result of surgery on the parathyroid glands (subtotal or total parathyroidectomy). Risk factors for severe hypocalcemia after subtotal parathyroidectomy include

• Severe preoperative hypercalcemia

• Removal of a large adenoma

• Elevated alkaline phosphatase

• Chronic kidney disease

Idiopathic hypoparathyroidism is an uncommon sporadic or inherited condition in which the parathyroid glands are absent or atrophied. It manifests in childhood. The parathyroid glands are occasionally absent and thymic aplasia and abnormalities of the arteries arising from the brachial arches (DiGeorge syndrome) are present. Other inherited forms include Addison's disease, autoimmune hypoparathyroidism associated with mucocutaneous candidiasis, and X-linked recessive idiopathic hypoparathyroidism.

Pseudohypoparathyroidism: Pseudohypoparathyroidism is an uncommon group of disorders characterized not by hormone deficiency but by target organ resistance to PTH. Complex genetic transmission of these disorders occurs.

Patients with type Ia pseudohypoparathyroidism (Albright's hereditary osteodystrophy) have a mutation in the stimulatory Gs-α1 protein of the adenylyl cyclase complex (*GNAS1*). The result is failure of normal renal phosphaturic response or increase in urinary cAMP to PTH. Patients are usually hypocalcemic as a result of hyperphosphatemia. Secondary hyperparathyroidism and hyperparathyroid bone disease can occur. Associated abnormalities include short stature, round facies, intellectual disability with calcification of the basal ganglia, shortened metacarpal and metatarsal bones, mild hypothyroidism, and other subtle endocrine abnormalities. Because only the maternal allele for *GNAS1* is expressed in the kidneys, patients whose abnormal gene is paternal, although they have many of the somatic features of the disease, do not have hypocalcemia, hyperphosphatemia, or secondary hyperparathyroidism; this

condition is sometimes described as pseudopseudohypoparathyroidism.

Less is known about type Ib pseudohypoparathyroidism. Affected patients have hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism but do not have the other associated abnormalities.

Type II pseudohypoparathyroidism is even less common than type I. In affected patients, exogenous PTH raises the urinary cAMP normally but does not raise serum Ca or urinary phosphate (PO_4). An intracellular resistance to cAMP has been proposed.

Vitamin D deficiency and dependency: Vitamin D deficiency and dependency are discussed in full elsewhere (see p. 41). Vitamin D is ingested in foods naturally high in vitamin D or fortified with it. It is also formed in the skin in response to sunlight. Vitamin D deficiency may result from inadequate dietary intake or decreased absorption due to hepatobiliary disease or intestinal malabsorption. It can also result from alterations in vitamin D metabolism as occur with certain drugs (eg, phenytoin, phenobarbital, rifampin) or decreased formation in the skin due to lack of exposure to sunlight. Aging also decreases skin synthetic capacity. Decreased skin synthesis is an important cause of acquired vitamin D deficiency among people who spend a great deal of time indoors, who live in high northern or southern latitudes, and who wear clothing that covers them completely. Accordingly, subclinical vitamin D deficiency is fairly common, especially during winter months in temperate climates among the elderly. The institutionalized elderly are at particular risk because of decreased skin synthetic capacity, undernutrition, and lack of sun exposure. In fact, most people with deficiency have both decreased skin synthesis and dietary deficiency (see also p. 41).

Type I vitamin D-dependent rickets (pseudovitamin D-deficiency rickets) is an autosomal recessive disorder involving a mutation in the gene encoding the 1-α-hydroxylase enzyme. Normally expressed in the kidney, 1-α-hydroxylase is needed to convert inactive vitamin D to the active form calcitriol.

In type II vitamin D-dependent rickets, target organs cannot respond to calcitriol. Vitamin D deficiency, hypocalcemia, and severe hypophosphatemia occur. Muscle weakness, pain, and typical bone deformities can occur.

Renal disease: Renal tubular disease, including acquired proximal renal tubular acidosis due to nephrotoxins (eg, heavy metals) and distal renal tubular acidosis, can cause severe hypocalcemia due to abnormal renal loss of Ca and decreased renal conversion to $1,25(OH)_2D$. Cadmium, in particular, causes hypocalcemia by injuring proximal tubular cells and interfering with vitamin D conversion.

Renal failure can result in hypocalcemia due to diminished formation of $1,25(OH)_2D$ from direct renal cell damage as well as suppression of 1-α-hydroxylase by hyperphosphatemia.

Other causes: Other causes of hypocalcemia include

- Mg depletion (can cause relative PTH deficiency and end-organ resistance to PTH action, usually when serum Mg concentrations are < 1.0 mg/dL [< 0.5 mmol/L]; Mg repletion increases PTH concentrations and improves renal Ca conservation)

- Acute pancreatitis (when lipolytic products released from the inflamed pancreas chelate Ca)

- Hypoproteinemia (reduces the protein-bound fraction of serum Ca; hypocalcemia due to diminished protein binding is asymptomatic—because ionized Ca is unchanged, this entity has been termed factitious hypocalcemia)

- Hungry bone syndrome (persistent hypocalcemia and hypophosphatemia occurring after surgical or medical correction of moderate to severe hyperparathyroidism in patients in whom serum Ca levels had been supported by high bone turnover induced by greatly elevated PTH—hungry bone syndrome has been described after parathyroidectomy, after renal transplantation, and rarely in patients with end-stage renal disease treated with calcimimetics)

- Septic shock (due to suppression of PTH release and decreased conversion of 25(OH)D to $1,25(OH)_2D$)

- Hyperphosphatemia (causes hypocalcemia by poorly understood mechanisms; patients with renal failure and subsequent PO_4 retention are particularly prone)

- Drugs including anticonvulsants (eg, phenytoin, phenobarbital) and rifampin, which alter vitamin D metabolism, and drugs generally used to treat hypercalcemia (see p. 847)

- Transfusion of > 10 units of citrate-anticoagulated blood and use of radiocontrast agents containing the divalent ion-chelating agent ethylenediaminetetraacetate (can decrease the concentration of bioavailable ionized Ca while total serum Ca concentrations remain unchanged)

- Infusion of gadolinium (may spuriously lower Ca concentration)

Although excessive secretion of calcitonin might be expected to cause hypocalcemia, low serum Ca concentrations rarely occur in patients with large amounts of circulating calcitonin due to medullary carcinoma of the thyroid.

Symptoms and Signs

Hypocalcemia is frequently asymptomatic. The presence of hypoparathyroidism is often suggested by the clinical manifestations of the underlying disorder (eg, short stature, round facies, intellectual disability, basal ganglia calcification in type Ia pseudohypoparathyroidism).

Major clinical manifestations of hypocalcemia are due to disturbances in cellular membrane potential, resulting in neuromuscular irritability.

Neurologic manifestations: Muscle cramps involving the back and legs are common. Insidious hypocalcemia may cause mild, diffuse encephalopathy and should be suspected in patients with unexplained dementia, depression, or psychosis. Papilledema occasionally occurs. Severe hypocalcemia with serum Ca < 7 mg/dL (< 1.75 mmol/L) may cause hyperreflexia, tetany, laryngospasm, or generalized seizures.

Tetany characteristically results from severe hypocalcemia but can result from reduction in the ionized fraction of serum Ca without marked hypocalcemia, as occurs in severe alkalosis. Tetany is characterized by the following:

- Sensory symptoms consisting of paresthesias of the lips, tongue, fingers, and feet

- Carpopedal spasm, which may be prolonged and painful

- Generalized muscle aching

- Spasm of facial musculature

Tetany may be overt with spontaneous symptoms or latent and requiring provocative tests to elicit. Latent tetany generally occurs at less severely decreased serum Ca concentrations: 7 to 8 mg/dL (1.75 to 2.20 mmol/L).

Chvostek's and Trousseau's signs are easily elicited at the bedside to identify latent tetany. Chvostek's sign is an involuntary twitching of the facial muscles elicited by a light tapping of the facial nerve just anterior to the exterior auditory meatus. It is present in ≤ 10% of healthy people and in most people with acute hypocalcemia but is often absent in chronic hypocalcemia. Trousseau's sign is the precipitation of carpopedal spasm by reduction of the blood supply to the hand with a tourniquet or BP cuff inflated to 20 mm Hg above systolic BP applied to the forearm for 3 min. Trousseau's sign also occurs in alkalosis, hypomagnesemia, hypokalemia, and hyperkalemia and in about 6% of people with no identifiable

electrolyte disturbance.

Other manifestations: Many other abnormalities may occur with chronic hypocalcemia, such as dry and scaly skin, brittle nails, and coarse hair. *Candida* infections occasionally occur in hypocalcemia but most commonly occur in patients with idiopathic hypoparathyroidism. Cataracts occasionally occur with long-standing hypocalcemia and are not reversible by correction of serum Ca.

Diagnosis

• Estimation or measurement of ionized Ca

• Sometimes further testing with Mg, PTH, PO_4, alkaline phosphatase, and vitamin D concentrations in blood and cAMP and PO_4 concentrations in urine

Hypocalcemia may be suspected in patients with characteristic neurologic manifestations or cardiac arrhythmias but is often found incidentally. Hypocalcemia is diagnosed by a total serum Ca concentration < 8.8 mg/dL (< 2.20 mmol/L). However, because low plasma protein can lower total, but not ionized, serum Ca, ionized Ca should be estimated based on albumin concentration (see Sidebar 97-2). Suspicion of low ionized Ca mandates its direct measurement, despite normal total serum Ca. Hypocalcemic patients should undergo measurement of renal function (eg, BUN, creatinine), serum PO_4, Mg, and alkaline phosphatase.

When no etiology (eg, alkalosis, renal failure, drugs, or massive blood transfusion) is obvious, further testing is needed (see Table 97-8). Additional testing begins with serum concentrations of Mg, PO_4, PTH, alkaline phosphatase, and occasionally vitamin D levels (25(OH)D, and 1,25$(OH)_2$D). Urinary PO_4 and cAMP concentrations are measured when pseudohypoparathyroidism is suspected.

PTH concentration should be measured as an assay of the intact molecule. Because hypocalcemia is the major stimulus for PTH secretion, PTH should be elevated in hypocalcemia. Thus,

• Low or even low-normal PTH concentrations are inappropriate and suggest hypoparathyroidism.

• An undetectable PTH concentration suggests idiopathic hypoparathyroidism.

• A high PTH concentration suggests pseudohypoparathyroidism or an abnormality of vitamin D metabolism.

Sidebar 97-2 Estimation of Ionized Calcium Concentration

Ionized Ca concentration can be estimated from routine laboratory tests, usually with reasonable accuracy. In hypoalbuminemia, measured serum Ca is often low, mainly reflecting a low concentration of protein-bound Ca, while ionized Ca can be normal. Measured total serum Ca decreases or increases by about 0.8 mg/dL (0.20 mmol/L) for every 1-g/dL decrease or increase in albumin. Thus, an albumin concentration of 2.0 g/dL (normal, 4.0 g/dL) should itself reduce measured serum Ca by 1.6 mg/dL. Similarly, increases in serum proteins, as occur in multiple myeloma, can raise total serum Ca. Acidosis increases ionized Ca by decreasing protein binding, whereas alkalosis decreases ionized Ca.

Hypoparathyroidism is further characterized by high serum PO_4 and normal alkaline phosphatase.

In type I pseudohypoparathyroidism, despite the presence of a high concentration of circulating PTH, urinary cAMP and urinary PO_4 are absent. Provocative testing by injection of parathyroid extract or recombinant human PTH fails to raise serum or urinary cAMP. Patients with type Ia pseudohypoparathyroidism frequently also have skeletal abnormalities, including short stature and shortened 1st, 4th, and 5th metacarpals. Patients with type Ib disease have renal manifestations without

skeletal abnormalities.

In vitamin D deficiency, osteomalacia or rickets may be present, usually with typical skeletal abnormalities on x-ray. Diagnosis of vitamin D deficiency and dependency and measurement of vitamin D concentrations are discussed on p. 42.

Severe hypocalcemia can affect the ECG. It typically shows prolongation of the QTc and ST intervals. Changes in repolarization, such as T-wave peaking or inversion, also occur. ECG may show arrhythmia or heart block occasionally in patients with severe hypocalcemia. However, evaluation of hypocalcemia does not mandate ECG testing.

Treatment

• IV Ca gluconate for tetany

• Oral Ca for postoperative hypoparathyroidism

• Oral Ca and vitamin D for chronic hypocalcemia

[**Table 97-8.** Typical Laboratory Test Results in Some Disorders Causing Hypocalcemia]

For tetany, Ca gluconate 10 mL of 10% solution IV over 10 min is given. Response can be dramatic but may last for only a few hours. Repeated boluses or a continuous infusion with 20 to 30 mL of 10% Ca gluconate in 1 L of 5% D/W over the next 12 to 24 h may be needed. Infusions of Ca are hazardous in patients receiving digoxin and should be given slowly and with continuous ECG monitoring. When tetany is associated with hypomagnesemia, it may respond transiently to Ca or K administration but is permanently relieved only by repletion of Mg, typically given as a 10% Mg sulfate ($MgSO_4$) solution (1 g/10 mL) IV, followed by oral Mg salts (eg, Mg gluconate 500 to 1000 mg po tid).

In transient hypoparathyroidism after thyroidectomy or partial parathyroidectomy, supplemental oral Ca may be sufficient; 1 to 2 g of elemental Ca/day may be given as Ca gluconate (90 mg elemental Ca/1 g) or Ca carbonate (400 mg elemental Ca/1 g). However, hypocalcemia may be particularly severe and prolonged after subtotal parathyroidectomy, particularly in patients with chronic kidney disease or in patients from whom a large tumor was removed. Prolonged parenteral administration of Ca may be necessary postoperatively; supplementation with as much as 1 g/day of elemental Ca (eg, 111 mL of Ca gluconate, which contains 90 mg elemental Ca/10 mL) may be required for 5 to 10 days before oral Ca and vitamin D are sufficient. Elevated serum alkaline phosphatase in such patients may be a sign of rapid uptake of Ca into bone. The need for large amounts of parenteral Ca usually does not fall until the alkaline phosphatase concentration begins to decrease.

In chronic hypocalcemia, oral Ca and occasionally vitamin D supplements are usually sufficient: 1 to 2 g of elemental Ca/day may be given as Ca gluconate or Ca carbonate. In patients without renal failure, vitamin D is given as a standard oral supplement (eg, cholecalciferol 800 IU once/day). Vitamin D therapy is not effective unless adequate dietary or supplemental Ca and PO_4 (see p. 851) are supplied.

For patients with renal failure, calcitriol or another $1,25(OH)_2D$ analog is used because these drugs require no renal metabolic alteration. Patients with hypoparathyroidism have difficulty converting cholecalciferol to its active form and also usually require calcitriol, usually 0.5 to 2 µg po once/day. Pseudohypoparathyroidism can occasionally be managed with oral Ca supplementation alone. When used, calcitriol requires 1 to 3 µg/day.

Vitamin D analogs include dihydrotachysterol (usually given orally at 0.8 to 2.4 once/day for a few days, followed by 0.2 to 1.0 mg once/day) and calcidiol (eg, 4000 to 6000 IU po once/wk). Use of vitamin D analogs, particularly the longer-acting calcidiol, can be complicated by vitamin D toxicity, with severe symptomatic hypercalcemia. Serum Ca concentration should be monitored weekly at first and then at 1- to 3-mo intervals after Ca concentrations have stabilized. The maintenance dose of calcitriol or its analog, dihydrotachysterol, usually decreases with time.

Hypercalcemia

Hypercalcemia is total serum Ca concentration > 10.4 mg/dL (> 2.60 mmol/L) or ionized serum Ca > 5.2 mg/dL (> 1.30 mmol/L). Principal causes include hyperparathyroidism, vitamin D toxicity, and cancer. Clinical features include polyuria, constipation, muscle weakness, confusion, and coma. Diagnosis is by serum ionized Ca and parathyroid hormone concentrations. Treatment to increase Ca excretion and reduce bone resorption of Ca involves saline, Na diuresis, and drugs such as pamidronate.

Etiology

Hypercalcemia usually results from excessive bone resorption. There are many causes of hypercalcemia (see
Table 97-9), but the most common are hyperparathyroidism and cancer.

Pathophysiology

Primary hyperparathyroidism is a generalized disorder resulting from excessive secretion of parathyroid hormone (PTH) by one or more parathyroid glands. It probably is the most common cause of hypercalcemia, particularly among patients who are not hospitalized. Incidence increases with age and is higher in postmenopausal women. It also occurs in high frequency ≥ 3 decades after neck irradiation. Familial and sporadic forms exist. Familial forms due to parathyroid adenoma occur in patients with other endocrine tumors (see p. 909). Primary hyperparathyroidism causes hypophosphatemia and excessive bone resorption. Although asymptomatic hypercalcemia is the most frequent presentation, nephrolithiasis is also common, particularly when hypercalciuria occurs due to long-standing hypercalcemia. Histologic examination shows a parathyroid adenoma in about 85% of patients with primary hyperparathyroidism, although it is sometimes difficult to distinguish an adenoma from a normal gland. About 15% of cases are due to hyperplasia of ≥ 2 glands. Parathyroid cancer occurs in < 1% of cases.

The syndrome of **familial hypocalciuric hypercalcemia (FHH)** is transmitted as an autosomal dominant trait. Most cases involve an inactivating mutation of the Ca-sensing receptor gene, resulting in higher concentrations of serum Ca being needed to inhibit PTH secretion. Subsequent PTH secretion induces renal phosphate (PO_4) excretion. Persistent hypercalcemia (usually asymptomatic), often from an early age; normal to slightly elevated concentrations of PTH; hypocalciuria; and hypermagnesemia occur. Renal function is normal, and nephrolithiasis is unusual. However, severe pancreatitis occasionally occurs. This syndrome, which is associated with parathyroid hyperplasia, is not relieved by subtotal parathyroidectomy.

Secondary hyperparathyroidism occurs most commonly in advanced chronic kidney

[**Table 97-9.** Principal Causes of Hypercalcemia]

disease when decreased formation of active vitamin D in the kidneys and other factors lead to hypocalcemia and chronic stimulation of PTH secretion. Hyperphosphatemia that develops in response to chronic kidney disease also contributes. Once established, hypercalcemia or normocalcemia may occur. The sensitivity of the parathyroid to Ca may be diminished because of pronounced glandular hyperplasia and elevation of the Ca set point (ie, the amount of Ca necessary to reduce secretion of PTH).

Tertiary hyperparathyroidism results in autonomous hypersecretion of PTH regardless of serum Ca concentration. Tertiary hyperparathyroidism generally occurs in patients with long-standing secondary hyperparathyroidism, as in patients with end-stage renal disease of several years' duration.

Cancer is a common cause of hypercalcemia, usually in hospitalized patients. Although there are several mechanisms, elevated serum Ca ultimately occurs as a result of bone resorption. Humoral hypercalcemia of cancer (ie, hypercalcemia with no or minimal bone metastases) occurs most commonly with squamous cell carcinoma, renal cell carcinoma, breast cancer, prostate cancer, and ovarian cancer. Many cases of humoral hypercalcemia of cancer were formerly attributed to ectopic production of PTH. However, some

of these tumors secrete a PTH-related peptide that binds to PTH receptors in both bone and kidney and mimics many of the effects of the hormone, including osteoclastic bone resorption. Hematologic cancers, most often multiple myeloma, but also certain lymphomas and lymphosarcomas, cause hypercalcemia by elaborating a group of cytokines that stimulate osteoclasts to resorb bone, resulting in osteolytic lesions, diffuse osteopenia, or both. Hypercalcemia may result from local elaboration of osteoclast-activating cytokines or prostaglandins, direct bone resorption by the metastatic tumor cells, or both.

Vitamin D toxicity can be caused by high concentrations of endogenous $1,25(OH)_2D$. Although serum concentrations are low in most patients with solid tumors, patients with lymphoma and T-cell leukemia sometimes have elevated concentrations due to dysregulation of the 1-α-hydroxylase enzyme present in tumor cells. Exogenous vitamin D in pharmacologic doses causes excessive bone resorption as well as increased intestinal Ca absorption, resulting in hypercalcemia and hypercalciuria (see p. 44).

Granulomatous disorders, such as sarcoidosis, TB, leprosy, berylliosis, histoplasmosis, and coccidioidomycosis, lead to hypercalcemia and hypercalciuria. In sarcoidosis, hypercalcemia and hypercalciuria seem to be due to unregulated conversion of 25(OH)D to $1,25(OH)_2D$, presumably due to expression of the 1-α-hydroxylase enzyme in mononuclear cells within sarcoid granulomas. Similarly, elevated serum concentrations of $1,25(OH)_2D$ have been reported in hypercalcemic patients with TB and silicosis. Other mechanisms must account for hypercalcemia in some instances, because depressed $1,25(OH)_2D$ concentrations occur in some patients with hypercalcemia and leprosy.

Immobilization, particularly complete prolonged bed rest in patients at risk (see Table 97-9), can result in hypercalcemia due to accelerated bone resorption. Hypercalcemia develops within days to weeks of onset of bed rest. Reversal of hypercalcemia occurs promptly on resumption of weight bearing. Young adults with several bone fractures and people with Paget's disease of bone are particularly prone to hypercalcemia when at bed rest.

Idiopathic infantile hypercalcemia (Williams syndrome—see Table 299-2 on p. 3003) is an extremely rare sporadic disorder with dysmorphic facial features, cardiovascular abnormalities, renovascular hypertension, and hypercalcemia. PTH and vitamin D metabolism are normal, but the response of calcitonin to Ca infusion may be abnormal.

In **milk-alkali syndrome**, excessive amounts of Ca and absorbable alkali are ingested, usually during self-treatment with Ca carbonate antacids for dyspepsia or to prevent osteoporosis, resulting in hypercalcemia, metabolic alkalosis, and renal insufficiency. The availability of effective drugs for peptic ulcer disease and osteoporosis has greatly reduced the incidence of this syndrome.

Symptoms and Signs

In mild hypercalcemia, many patients are asymptomatic. Clinical manifestations of hypercalcemia include constipation, anorexia, nausea and vomiting, abdominal pain, and ileus. Impairment of the renal concentrating mechanism leads to polyuria, nocturia, and polydipsia. Elevation of serum Ca > 12 mg/dL (> 3.00 mmol/L) can cause emotional lability, confusion, delirium, psychosis, stupor, and coma. Hypercalcemia may cause neuromuscular symptoms, including skeletal muscle weakness. Hypercalciuria with nephrolithiasis is common. Less often, prolonged or severe hypercalcemia causes reversible acute renal failure or irreversible renal damage due to nephrocalcinosis (precipitation of Ca salts within the kidney parenchyma). Peptic ulcers and pancreatitis may occur in patients with hyperparathyroidism for reasons that are not related to hypercalcemia.

Severe hypercalcemia causes a shortened QT_c interval on ECG, and arrhythmias may occur, particularly in patients taking digoxin. Hypercalcemia > 18 mg/dL (> 4.50 mmol/L) may cause shock, renal failure, and death.

Diagnosis

• Total serum Ca concentration

- Chest x-ray; measurement of electrolytes, BUN, creatinine, ionized Ca, PO_4, and alkaline phosphatase; and serum protein immunoelectrophoresis to determine the cause

- Sometimes PTH and urinary excretion of Ca with or without PO_4

Hypercalcemia is diagnosed by a serum Ca concentration > 10.4 mg/dL (> 2.60 mmol/L) or ionized serum Ca > 5.2 mg/dL (> 1.30 mmol/L). The condition is frequently discovered during routine laboratory screening. Serum Ca can be artifactually elevated (see Table 97-10). Hypercalcemia can also be masked by low serum protein. When protein and albumin are abnormal and when ionized hypercalcemia is suspected because of clinical findings (eg, because of symptoms of hypercalcemia), ionized serum Ca should be measured.

Initial evaluation: Initial evaluation should include a review of the history, particularly of past serum Ca concentration; physical examination; a chest x-ray; and laboratory studies, including electrolytes, BUN, creatinine, ionized Ca, PO_4, alkaline phosphatase, and serum protein immunoelectrophoresis. The cause is apparent from clinical data and results of these tests in ≥ 95% of patients. Patients without an obvious cause of hypercalcemia after this evaluation should undergo measurement of intact PTH and 24-h urinary Ca. When hyperparathyroidism is suspected, PO_4 renal excretion is often measured.

Asymptomatic hypercalcemia that has been present for years or is present in several family members raises the possibility of FHH. Primary hyperparathyroidism generally manifests late in life but can be present for several years before symptoms occur. When no cause is obvious, concentrations of serum Ca < 11 mg/dL (< 2.75 mmol/L) suggest hyperparathyroidism or other nonmalignant causes, whereas concentration > 13 mg/dL (> 3.25 mmol/L) suggest cancer.

Measurement of intact PTH levels help differentiate PTH-mediated hypercalcemia (eg, caused by hyperparathyroidism or FHH), in which PTH levels are high or high-normal,

[**Table 97-10.** Laboratory and Clinical Findings in Some Disorders Causing Hypercalcemia]

from most other (PTH-independent) causes. In PTH-independent causes, levels are usually < 20 pg/mL.

The chest x-ray is particularly helpful, revealing most granulomatous disorders, such as TB, sarcoidosis, and silicosis, as well as primary lung cancer and lytic and Paget's lesions in bones of the shoulder, ribs, and thoracic spine.

Chest and bone (eg, skull, extremity) x-rays can also show the bony effects of secondary hyperparathyroidism, most commonly in long-term dialysis patients. In osteitis fibrosa cystica (often due to primary hyperparathyroidism), increased osteoclastic activity from over-stimulation by PTH causes rarefaction of bone with fibrous degeneration and cyst and fibrous nodule formation. Because characteristic bone lesions occur only with relatively advanced disease, bone x-rays are recommended only for symptomatic patients. X-rays typically show bone cysts, a heterogeneous appearance of the skull, and subperiosteal resorption of bone in the phalanges and distal clavicles.

Hyperparathyroidism: In hyperparathyroidism, the serum Ca is rarely > 12 mg/dL (> 3.00 mmol/L), but the ionized serum Ca is almost always elevated. Low serum PO_4 concentration suggests hyperparathyroidism, especially when coupled with elevated PO_4 renal excretion. When hyperparathyroidism results in increased bone turnover, serum alkaline phosphatase is frequently increased. Increased intact PTH, particularly inappropriate elevation (ie, a high concentration in the absence of hypocalcemia) or an inappropriate high-normal concentration (ie, despite hypercalcemia), is diagnostic. Urinary Ca excretion is usually normal or high in hyperparathyroidism. Primary hyperparathyroidism is suggested by an absence of a family history of endocrine neoplasia, childhood neck irradiation, or other obvious cause. Chronic kidney disease suggests the presence of secondary hyperparathyroidism, but primary hyperparathyroidism can also be present. In patients with chronic kidney disease, high serum Ca and normal serum PO_4 suggest primary hyperparathyroidism, whereas elevated PO_4 suggests secondary hyperparathyroidism.

The need for localization of parathyroid tissue before surgery on the parathyroid(s) is controversial. High-resolution CT with or without CT-guided biopsy and immunoassay of thyroid venous drainage, MRI, high-resolution ultrasonography, digital subtraction angiography, and thallium-201-technetium-99 scanning all have been used and are highly accurate, but they have not improved the usually high cure rate of parathyroidectomy done by experienced surgeons. Technetium-99 sestamibi, a newer radionuclide agent for parathyroid imaging, is more sensitive and specific than older agents and may be useful for identifying solitary adenomas.

For residual or recurrent hyperparathyroidism after initial parathyroid surgery, imaging is necessary and may reveal abnormally functioning parathyroid glands in unusual locations throughout the neck and mediastinum. Technetium-99 sestamibi is probably the most sensitive imaging test. Use of several imaging studies (MRI, CT, or high-resolution ultrasonography in addition to technetium-99 sestamibi) before repeat parathyroidectomy is sometimes necessary.

Cancer: A serum Ca > 13 mg/dL (> 3.00 mmol/L) suggests some cause of hypercalcemia other than hyperparathyroidism. Urinary Ca excretion is usually normal or high in cancer. In humoral hypercalcemia of cancer, PTH is often decreased or undetectable; PO_4 is often decreased; and metabolic alkalosis, hypochloremia, and hypoalbuminemia are often present. Suppressed PTH differentiates humoral hypercalcemia of cancer from primary hyperparathyroidism. Humoral hypercalcemia of cancer can also be diagnosed by detection of PTH-related peptide in serum.

Multiple myeloma is suggested by simultaneous anemia, azotemia, and hypercalcemia or by the presence of a monoclonal gammopathy. Myeloma is confirmed by bone marrow examination.

FHH: FHH should be considered in patients with hypercalcemia and elevated or high-normal intact PTH levels. FHH is distinguished from primary hyperparathyroidism by the early age of onset, frequent occurrence of hypermagnesemia, and presence of hypercalcemia without hypercalciuria in other family members. The fractional excretion of Ca (ratio of Ca clearance to creatinine clearance) is low (< 1%) in FHH; it is almost always elevated (1 to 4%) in primary hyperparathyroidism. Intact PTH can be elevated or normal, perhaps reflecting altered feedback regulation of the parathyroid glands.

Milk-alkali syndrome: In addition to a history of increased intake of Ca antacids, milk-alkali syndrome is recognized by the combination of hypercalcemia, metabolic alkalosis, and, occasionally, azotemia with hypocalciuria. The diagnosis can be confirmed when the serum Ca concentration rapidly returns to normal when Ca and alkali ingestion stops, although renal insufficiency can persist when nephrocalcinosis is present. Circulating PTH usually is suppressed.

Other causes: In hypercalcemia due to sarcoidosis, other granulomatous disorders, and some lymphomas, serum concentration of $1,25(OH)_2D$ may be elevated. Vitamin D toxicity is also characterized by elevated $1,25(OH)_2D$ concentration. In other endocrine causes of hypercalcemia, such as thyrotoxicosis and Addison's disease, typical laboratory findings of the underlying disorder help establish the diagnosis. When Paget's disease is suspected, plain x-rays (see p. 361) are done first and may show characteristic abnormalities.

Treatment

- Oral PO_4 for serum Ca < 11.5 mg/dL with mild symptoms and no kidney disease
- IV saline and furosemide for more rapid correction for serum Ca < 18 mg/dL
- Bisphosphonates or other Ca-lowering drugs for serum Ca < 18 mg/dL and > 11.5 mg/dL or moderate symptoms
- Hemodialysis for serum Ca > 18 mg/dL
- Surgical removal for moderate, progressive primary hyperparathyroidism and sometimes for mild disease

• PO_4 restriction and binders and sometimes calcitriol for secondary hyperparathyroidism

There are 4 main strategies for lowering serum Ca: • Decrease intestinal Ca absorption

• Increase urinary Ca excretion

• Decrease bone resorption

• Remove excess Ca through dialysis

The treatment used depends on both the degree and the cause of hypercalcemia.

Mild hypercalcemia: In mild hypercalcemia (serum Ca < 11.5 mg/dL [< 2.88 mmol/L]), in which symptoms are mild, treatment is deferred pending definitive diagnosis. After diagnosis, the underlying disorder is treated. When symptoms are significant, treatment aimed at lowering serum Ca is necessary. Oral PO_4 can be used. When taken with meals, it binds some Ca, preventing its absorption. A starting dose is 250 mg of elemental PO_4 (as Na or K salt) qid. The dose can be increased to 500 mg qid prn unless diarrhea develops. Another treatment is increasing urinary Ca excretion by giving isotonic saline plus a loop diuretic. Initially, 1 to 2 L of saline is given over 2 to 4 h unless significant heart failure is present, because nearly all patients with significant hypercalcemia are hypovolemic. Furosemide 20 to 40 mg IV q 2 to 4 h is given as needed to maintain a urine output of roughly 250 mL/h (monitored hourly). Care must be taken to avoid volume depletion. K and Mg are monitored as often as every 4 h during treatment and replaced IV as needed to avoid hypokalemia and hypomagnesemia. Serum Ca begins to decrease in 2 to 4 h and falls to nearnormal within 24 h.

Moderate hypercalcemia: Moderate hypercalcemia (serum Ca > 11.5 mg/dL [< 2.88 mmol/L] and < 18 mg/dL [< 4.51 mmol/L]) can be treated with isotonic saline and a loop diuretic as is done for mild hypercalcemia or, depending on its cause, agents that decrease bone resorption (usually bisphosphonates, calcitonin, or infrequently plicamycin or gallium nitrate), corticosteroids, or chloroquine.

Bisphosphonates inhibit osteoclasts. They are usually the drugs of choice for cancer-associated hypercalcemia. Pamidronate can be given for cancer-associated hypercalcemia as a one-time dose of 30 to 90 mg IV, repeated only after 7 days. It lowers serum Ca for ≤ 2 wk. Zoledronate can also be given in doses of 4 to 8 mg IV and lowers serum Ca very effectively for an average of > 40 days. Ibandronate 4 to 6 mg IV can be given for cancer-associated hypercalcemia; it is effective for about 14 days. Etidronate 7.5 mg/kg IV once/day for 3 to 5 days is used to treat Paget's disease and cancer-associated hypercalcemia. Maintenance dosage is 20 mg/kg po once/day, but the dose must be reduced when GFR is low. Repetitive use of IV bisphosphonates to treat hypercalcemia associated with metastatic bone disease or myeloma has been associated with osteonecrosis of the jaw. Some reports suggest this finding may be more common with zoledronate. Renal toxicity has been reported in patients receiving zoledronate. Oral bisphosphonates (eg, alendronate or risedronate) can be given to maintain Ca in the normal range but are not generally used for treating hypercalcemia acutely.

Calcitonin (thyrocalcitonin) is a rapidly acting peptide hormone normally secreted in response to hypercalcemia by the C cells of the thyroid. Calcitonin seems to lower serum Ca by inhibiting osteoclastic activity. A dosage of 4 to 8 IU/kg sc q 12 h of salmon calcitonin is safe. Its usefulness in the treatment of cancer-associated hypercalcemia is limited by its short duration of action with the development of tachyphylaxis (often after about 48 h) and by the lack of response in ≥ 40% of patients. However, the combination of salmon calcitonin and prednisone may control serum Ca for several months in some patients with cancer. If calcitonin stops working, it can be stopped for 2 days (while prednisone is continued) and then resumed.

Corticosteroids (eg, prednisone 20 to 40 mg po once/day) can help control hypercalcemia as adjunctive therapy by decreasing calcitriol production and thus intestinal Ca absorption in most patients with vitamin D toxicity, idiopathic hypercalcemia of infancy, and sarcoidosis. Some patients with myeloma, lymphoma, leukemia, or metastatic cancer require 40 to 60 mg of prednisone once/day. However, > 50% of such patients fail to respond to corticosteroids, and response, when it occurs, takes several days; thus, other

treatment usually is necessary.

Chloroquine PO_4 500 mg po once/day inhibits $1,25(OH)_2D$ synthesis and reduces serum Ca concentration in patients with sarcoidosis. Routine ophthalmologic surveillance (eg, retinal examinations every 6 to 12 mo) is mandatory to detect dose-related retinal damage.

Plicamycin 25 µg/kg IV once/day in 50 mL of 5% D/W over 4 to 6 h is effective in patients with hypercalcemia due to cancer but is rarely used because other treatments are safer.

Gallium nitrate is also effective in hypercalcemia due to cancer but is used infrequently because of renal toxicity and limited clinical experience.

Severe hypercalcemia: In severe hypercalcemia (serum Ca > 18 mg/dL [> 4.50 mmol/L] or with severe symptoms), hemodialysis with low-Ca dialysate may be needed in addition to other treatments. Although there is no completely satisfactory way to correct severe hypercalcemia in patients with renal failure, hemodialysis is probably the safest and most reliable short-term treatment.

IV PO_4 (disodium PO_4 or monopotassium PO_4) should be used only when hypercalcemia is life threatening and unresponsive to other methods and when short-term hemodialysis is not possible. No more than 1 g should be given IV in 24 h; usually 1 or 2 doses over 2 days lower serum Ca for 10 to 15 days. Soft-tissue calcification and acute renal failure may result. (NOTE: IV infusion of Na sulfate is even more hazardous and less effective than PO_4 infusion and should not be used.)

Hyperparathyroidism: Treatment for hyperparathyroidism depends on severity.

Patients with **asymptomatic primary hyperparathyroidism** with no indications for surgery may be treated conservatively with methods to ensure that serum Ca concentrations remain low. Patients should remain active (ie, avoid immobilization that could exacerbate hypercalcemia), follow a low-Ca diet, drink plenty of fluids to minimize the chance of nephrolithiasis, and avoid drugs that can raise serum Ca, such as thiazide diuretics. Serum Ca and renal function are monitored every 6 mo. Bone density is monitored every 12 mo. However, subclinical bone disease, hypertension, and longevity are concerns. Osteoporosis is treated with bisphosphonates.

Surgery is indicated for patients with symptomatic or progressive hypoparathyroidism. The indications for surgery in patients with asymptomatic, primary hyperparathyroidism are controversial. Surgical parathyroidectomy increases bone density and may have modest effects on some quality of life symptoms, but most patients do not have progressive deterioration in biochemical abnormalities or bone density. Still, concerns about hypertension and longevity remain. Many experts recommend surgery in the following circumstances:

• Serum Ca 1 mg/dL (0.25 mmol/L) greater than the upper limits of normal Calciuria > 400 mg/day (> 10 mmol/day)

• Creatinine clearance 30% less than that of age-matched controls

Peak bone density at the hip, lumbar spine, or radius 2.5 standard deviations below controls (T score = -2.5)

Age < 50 yr

• The possibility of poor adherence with follow-up

Surgery consists of removal of adenomatous glands. PTH concentration can be measured before and after removal of the presumed abnormal gland using rapid assays. A fall of 50% or more 10 min after removal of the adenoma indicates successful treatment. In patients with disease of > 1 gland, several glands are removed, and often a small portion of a normalappearing parathyroid gland is reimplanted in the belly of the sternocleidomastoid muscle or subcutaneously in the forearm to prevent

hypoparathyroidism. Parathyroid tissue is also occasionally preserved using cryopreservation to allow for later autologous transplantation in case persistent hypoparathyroidism develops.

When hyperparathyroidism is mild, the serum Ca concentration drops to just below normal within 24 to 48 h after surgery; serum Ca must be monitored. In patients with severe osteitis fibrosa cystica, prolonged, symptomatic hypocalcemia may occur postoperatively unless 10 to 20 g elemental Ca is given in the days before surgery. Even with preoperative Ca administration, large doses of Ca and vitamin D may be required (see p. 841) while bone Ca is repleted.

Hyperparathyroidism in renal failure is usually secondary. Measures used for treatment can also be used for prevention. One aim is to prevent hyperphosphatemia. Treatment combines dietary PO_4 restriction and PO_4-binding agents, such as Ca carbonate or sevelamer. Despite the use of PO_4 binders, dietary restriction of PO_4 is needed. Aluminum-containing compounds have been used to limit PO_4 concentration, but they should be avoided, especially in patients receiving long-term dialysis, to prevent aluminum accumulation in bone resulting in severe osteomalacia. Vitamin D administration is potentially hazardous in renal failure because it can increase PO_4 absorption and contribute to hypercalcemia; administration requires frequent monitoring of Ca and PO_4. Treatment should be limited to patients with any of the following:

• Symptomatic osteomalacia (unrelated to aluminum)

• Secondary hyperparathyroidism

• Postparathyroidectomy hypocalcemia

Although oral calcitriol is often given along with oral Ca to suppress secondary hyperparathyroidism, the results are variable in patients with end-stage renal disease. The parenteral form of calcitriol, or vitamin D analogs such as paricalcitol, may better prevent secondary hyperparathyroidism in such patients, because the higher attained serum concentration of $1,25(OH)_2D$ directly suppresses PTH release. Simple osteomalacia may respond to 0.25 to 0.5 µg once/day of oral calcitriol, whereas correction of postparathyroidectomy hypocalcemia may require prolonged administration of as much as 2 µg of calcitriol once/day and ≥ 2 g of elemental Ca/day. The calcimimetic, cinacalcet, modulates the set point of the Ca-sensing receptor on parathyroid cells and decreases PTH concentration in dialysis patients without increasing serum Ca. In patients with osteomalacia caused by having taken large amounts of aluminum-containing PO_4 binders, removal of aluminum with deferoxamine is necessary before calcitrol administration reduces bone lesions.

FHH: Although FHH results from histologically abnormal parathyroid tissue, the response to subtotal parathyroidectomy is unsatisfactory. Because overt clinical manifestations are rare, drug therapy is not routinely indicated.

Disorders of Phosphate Concentration

Phosphorus is one of the most abundant elements in the human body. Most phosphorus in the body is complexed with O_2 as phosphate (PO_4). About 85% of the about 500 to 700 g of PO_4 in the body is contained in bone, where it is an important constituent of crystalline hydroxyapatite. In soft tissues, PO_4 is mainly found in the intracellular compartment as an integral component of several organic compounds, including nucleic acids and cell membrane phospholipids. PO_4 is also involved in aerobic and anaerobic energy metabolism. RBC 2,3-diphosphoglycerate (2,3-DPG) plays a crucial role in O_2 delivery to tissue. Adenosine diphosphate (ADP) and ATP contain PO_4 and use chemical bonds between PO_4 groups to store energy. Inorganic PO_4 is a major intracellular anion but is also present in plasma. The normal serum inorganic PO_4 concentration in adults ranges from 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L). PO_4 concentration is 50% higher in infants and 30% higher in children, possibly because of the important roles these PO_4-dependent processes play in growth.

The typical American diet contains about 800 to 1500 mg of PO_4. The amount in the stool varies depending on the amount of PO_4 binding compounds (mainly Ca) in the diet. Also, like Ca, GI PO_4 absorption is enhanced by vitamin D. Renal PO_4 excretion roughly equals GI absorption to maintain PO_4 balance. PO_4 depletion can occur in various disorders and normally results in conservation of PO_4 by the kidneys. Bone PO_4 serves as a reservoir, which can buffer changes in plasma and intracellular PO_4.

Hypophosphatemia

Hypophosphatemia is serum phosphate (PO_4) concentration < 2.5 mg/dL (0.81 mmol/L). Causes include alcoholism, burns, starvation, and diuretic use. Clinical features include muscle weakness, respiratory failure, and heart failure; seizures and coma can occur. Diagnosis is by serum PO_4 concentration. Treatment consists of PO_4 supplementation.

Etiology

Hypophosphatemia occurs in 2% of hospitalized patients but is more prevalent in certain populations (eg, it occurs in up to 10% of hospitalized patients with alcoholism).

Hypophosphatemia has numerous causes, but clinically significant acute hypophosphatemia occurs in relatively few clinical settings, including the following:

- The recovery phase of diabetic ketoacidosis
- Acute alcoholism
- Severe burns
- When receiving TPN
- Refeeding after prolonged undernutrition
- Severe respiratory alkalosis

Acute severe hypophosphatemia with serum PO_4 < 1 mg/dL (< 0.32 mmol/L) is most often caused by transcellular shifts of PO_4, often superimposed on chronic PO_4 depletion.

Chronic hypophosphatemia usually is the result of decreased renal PO_4 reabsorption. Causes include the following:

- Hyperparathyroidism
- Other hormonal disturbances, such as Cushing's syndrome and hypothyroidism
- Electrolyte disorders, such as hypomagnesemia and hypokalemia
- Theophylline intoxication
- Long-term diuretic use

Severe chronic hypophosphatemia usually results from a prolonged negative PO_4 balance. Causes include

- Chronic starvation or malabsorption, especially when combined with vomiting or copious diarrhea
- Long-term ingestion of large amounts of PO_4-binding aluminum, usually in the form of antacids

Ingestion of aluminum is particularly prone to cause PO_4 depletion when combined with decreased dietary intake and dialysis losses of PO_4 in patients with end-stage renal disease.

Symptoms and Signs

Although hypophosphatemia usually is asymptomatic, anorexia, muscle weakness, and osteomalacia can occur in severe chronic depletion. Serious neuromuscular disturbances may occur, including progressive encephalopathy, seizures, coma, and death. The muscle weakness of profound hypophosphatemia may be accompanied by rhabdomyolysis, especially in acute alcoholism. Hematologic disturbances of profound hypophosphatemia include hemolytic anemia, decreased release of O_2 from Hb, and impaired leukocyte and platelet function.

Diagnosis

• Serum PO_4 levels

Hypophosphatemia is diagnosed by a serum PO_4 concentration < 2.5 mg/dL (< 0.81 mmol/L). Most causes of hypophosphatemia (eg, diabetic ketoacidosis, burns, refeeding) are readily apparent. Testing to diagnose the cause is done when clinically indicated (eg, suggestive liver function test results or signs of cirrhosis in patients with suspected alcoholism).

Treatment

• Oral PO_4 replacement

• IV PO_4 when serum PO_4 is < 0.5 mEq/L or symptoms are severe

Oral treatment: Treatment of the underlying disorder and oral PO_4 replacement are usually adequate in asymptomatic patients, even when the serum concentration is very low. PO_4 can be given in doses up to about 1 g po tid in tablets containing Na or K PO_4. Oral Na or K PO_4 may be poorly tolerated because of diarrhea. Ingestion of 1 L of low-fat or skim milk provides 1 g of PO_4 and may be more acceptable. Removal of the cause of hypophosphatemia may include stopping PO_4-binding antacids or diuretics or correcting hypomagnesemia.

Parenteral treatment: Parenteral PO_4 is usually given IV. It should be administered in any of the following circumstances:

• When serum PO_4 is < 0.5 mEq/L (< 0.16 mmol/L)

• Rhabdomyolysis, hemolysis, or CNS symptoms are present

• Oral replacement is not feasible due to underlying disorder

IV administration of KPO_4 (as buffered mix of K_2HPO_4 and KH_2PO_4) is relatively safe when renal function is well preserved. $NaPO_4$ (rather than KPO_4) preparations generally should be used in patients with impaired renal function. The usual parenteral dose of KPO_4 is 2.5 mg (0.08 mmol)/kg IV over 6 h. Patients with alcoholism may require ≥ 1 g/day during TPN; supplemental PO_4 is stopped when oral intake is resumed. Serum Ca and PO_4 concentrations should be monitored during therapy, particularly when PO_4 is given IV or to patients with impaired renal function. In most cases, no more than 7 mg/kg (about 500 mg for a 70-kg adult) of PO_4 should be given over 6 h. Close monitoring is done and more rapid rates of PO_4 administration should be avoided to prevent hypocalcemia, hyperphosphatemia, and metastatic calcification due to excessive Ca × PO_4 product.

Hyperphosphatemia

Hyperphosphatemia is serum phosphate (PO_4) concentration > 4.5 mg/dL (> 1.46 mmol/L). Causes include chronic renal failure, hypoparathyroidism, and metabolic or respiratory acidosis. Clinical features may be due to accompanying hypocalcemia and include tetany. Diagnosis is by serum PO_4. Treatment includes restriction of PO_4 intake and administration of PO_4-binding antacids, such as Ca carbonate.

The usual cause of hyperphosphatemia is a decrease in renal excretion of PO_4. Advanced renal insufficiency (GFR < 30 mL/min) reduces excretion sufficiently to increase serum PO_4. Defects in renal excretion of PO_4 in the absence of renal failure also occur in pseudohypoparathyroidism and hypoparathyroidism. Hyperphosphatemia can also occur with excessive oral PO_4 administration and occasionally with overzealous use of enemas containing PO_4.

Hyperphosphatemia occasionally results from a transcellular shift of PO_4 into the extracellular space that is so large that the renal excretory capacity is overwhelmed. This transcellular shift occurs most frequently in diabetic ketoacidosis (despite total body PO_4 depletion), crush injuries, and nontraumatic rhabdomyolysis as well as in overwhelming systemic infections and tumor lysis syndrome.

Major causes of hyperphosphatemia include

- GFR < 30 mL/min
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Excessive oral PO_4 administration
- Overzealous use of enemas containing PO_4
- Shifts of PO_4 into the extracellular space (eg, in diabetic ketoacidosis, rhabdomyolysis, overwhelming systemic infections, and tumor lysis syndrome)

Hyperphosphatemia plays a critical role in the development of secondary hyperparathyroidism and renal osteodystrophy in patients with advanced chronic kidney disease as well as in patients on dialysis. Lastly, hyperphosphatemia can be spurious in cases of hyperproteinemia (multiple myeloma or Waldenstrom's macroglobulinemia), hyperlipidemia, hemolysis, or hyperbilirubinemia.

Hyperphosphatemia can lead to hypocalcemia by causing Ca and PO_4 precipitation into soft tissues, especially when the serum Ca × PO_4 product is chronically > 55 in patients with chronic kidney disease.

Symptoms and Signs

Most patients with hyperphosphatemia are asymptomatic, although symptoms of hypocalcemia, including tetany, can occur when concomitant hypocalcemia is present. Soft-tissue calcifications are common among patients with chronic kidney disease.

Diagnosis

- PO_4 concentration > 4.5 mg/dL (> 1.46 mmol/L)

Hyperphosphatemia is diagnosed by PO_4 concentration. When the etiology is not obvious (eg, rhabdomyolysis, tumor lysis syndrome, renal failure, overingestion of PO_4,-containing laxatives), additional evaluation is warranted to exclude hypoparathyroidism or pseudohypoparathyroidism, which is end-organ resistance to parathyroid hormone (PTH—see p. 839). False elevation of serum PO_4 also

should be excluded by measuring serum protein, lipid, and bilirubin concentrations.

Treatment

• PO_4 restriction

• PO_4 binders

The mainstay of treatment in patients with renal failure is reduction of PO_4 intake, which is usually accomplished with avoidance of foods containing high amounts of PO_4 and with use of PO_4-binding drugs taken with meals. Because of the possibility of aluminum-related osteomalacia, Ca carbonate and Ca acetate replace aluminum-containing antacids in patients with end-stage renal disease. Because of the possibility of excessive Ca × PO_4 product causing vascular calcification in dialysis patients taking Ca-containing binders, a PO_4-binding resin without Ca, sevelamer, is widely used in dialysis patients in doses of 800 to 2400 mg tid with meals. Lanthanum carbonate, another PO_4 binder that lacks Ca, can also be used in dialysis patients. It is given in doses of 500 to 1000 mg tid with meals.

Disorders of Magnesium Concentration

Mg is the 4th most plentiful cation in the body. A 70-kg adult has about 2000 mEq of Mg. About 50% is sequestered in bone and is not readily exchangeable with Mg in other compartments. The ECF contains only about 1% of total body Mg. The remainder resides in the intracellular compartment. Normal serum Mg concentration ranges from 1.4 to 2.1 mEq/L (0.70 to 1.05 mmol/L).

The maintenance of serum Mg concentration is largely a function of dietary intake and effective renal and intestinal conservation. Within 7 days of initiation of a Mg-deficient diet, renal and stool Mg excretion each fall to about 1 mEq/day (0.5 mmol/day).

About 70% of serum Mg is ultrafiltered (filtered through minute pores) by the kidney; the remainder is bound to protein. Protein binding of Mg is pH dependent. Serum Mg concentration is not closely related to either total body Mg or intracellular Mg content. However, severe serum hypomagnesemia may reflect diminished total body Mg.

Many enzymes are activated by or are dependent on Mg. Mg is required by all enzymatic processes involving ATP and by many of the enzymes involved in nucleic acid metabolism. Mg is required for thiamine pyrophosphate cofactor activity and seems to stabilize the structure of macromolecules such as DNA and RNA. Mg is also related to Ca and K metabolism in an intimate but poorly understood way.

Hypomagnesemia

Hypomagnesemia is serum Mg concentration < 1.4 mEq/L (< 0.70 mmol/L). Causes include inadequate Mg intake and absorption or increased excretion due to hypercalcemia or drugs such as furosemide. Clinical features are often due to accompanying hypokalemia and hypocalcemia and include lethargy, tremor, tetany, seizures, and arrhythmias. Treatment is with Mg replacement.

Serum Mg concentration, even when free Mg ion is measured, may be normal even with decreased intracellular or bone Mg stores. Mg depletion usually results from inadequate intake plus impairment of renal conservation or GI absorption. There are numerous causes of clinically significant Mg deficiency (see
Table 97-11).

Symptoms and Signs

Clinical manifestations are anorexia, nausea, vomiting, lethargy, weakness, personality change, tetany (eg, positive Trousseau's or Chvostek's sign or spontaneous carpopedal spasm, hyperreflexia), and tremor and muscle fasciculations. The neurologic signs, particularly tetany, correlate with development of

concomitant hypocalcemia, hypokalemia, or both. Myopathic potentials are found on electromyography but are also compatible with hypocalcemia or hypokalemia. Severe hypomagnesemia may cause generalized tonicclonic seizures, especially in children.

Diagnosis

• Considered in patients with risk factors and with unexplained hypocalcemia or hypokalemia

• Serum Mg concentration < 1.4 mEq/L (< 0.70 mmol/L)

Hypomagnesemia is diagnosed by a serum Mg concentration. Severe hypomagnesemia usually results in concentrations of < 1.0 mEq/L (< 0.50 mmol/L). Associated hypocalcemia and hypocalciuria are common. Hypokalemia with increased urinary K excretion and metabolic alkalosis may be present. Mg deficiency should be suspected even when serum Mg concentration is normal in patients with unexplained hypocalcemia or refractory hypokalemia. Mg deficiency should also be suspected in patients with unexplained neurologic symptoms and alcoholism, with chronic diarrhea, or after cyclosporine, cisplatinum-based chemotherapy or prolonged therapy with amphotericin B or aminoglycosides.

[**Table 97-11.** Causes of Hypomagnesemia]

Treatment

• Oral Mg salts

• IV or IM Mg sulfate for severe hypomagnesemia or inability to tolerate or adhere to oral therapy

Treatment with Mg salts is indicated when Mg deficiency is symptomatic or persistently < 1 mEq/L (< 0.50 mmol/L). Patients with alcoholism are treated empirically. In such cases, deficits approaching 12 to 24 mg/kg are possible. About twice the amount of the estimated deficit should be given in patients with intact renal function, because about 50% of the administered Mg is excreted in urine. Oral Mg salts (eg, Mg gluconate 500 to 1000 mg po tid) are given for 3 to 4 days. Oral treatment is limited by the onset of diarrhea. Parenteral administration is reserved for patients with severe, symptomatic hypomagnesemia who cannot tolerate oral drugs. Sometimes a single injection is given in patients with alcoholism who are unlikely to adhere to ongoing oral therapy. When Mg must be replaced parenterally, a 10% Mg sulfate ($MgSO_4$) solution (1 g/10 mL) is available for IV use and a 50% solution (1 g/2 mL) is available for IM use. The serum Mg concentration should be monitored frequently during Mg therapy, particularly when Mg is given to patients with renal insufficiency or in repeated parenteral doses. In these patients, treatment is continued until a normal serum Mg concentration is achieved.

In severe, symptomatic hypomagnesemia (eg, Mg < 1 mEq/L [< 0.5 mmol/L] with seizures or other severe symptoms), 2 to 4 g of $MgSO_4$ IV is given over 5 to 10 min. When seizures persist, the dose may be repeated up to a total of 10 g over the next 6 h. In patients in whom seizures stop, 10 g in 1 L of 5% D/W can be infused over 24 h, followed by up to 2.5 g q 12 h to replace the deficit in total Mg stores and prevent further drops in serum Mg. When serum Mg is ≤ 1 mEq/L (< 0.5 mmol/L) but symptoms are less severe, $MgSO_4$ may be given IV in 5% D/W at a rate of 1 g/h as slow infusion for up to 10 h. In less severe cases of hypomagnesemia, gradual repletion may be achieved by administration of smaller parenteral doses over 3 to 5 days until the serum Mg concentration is normal.

Hypermagnesemia

Hypermagnesemia is a serum Mg concentration > 2.1 mEq/L (> 1.05 mmol/L). The major cause is renal failure. Symptoms include hypotension, respiratory depression, and cardiac arrest. Diagnosis is by serum Mg concentration. Treatment includes IV administration of Ca gluconate and possibly furosemide; hemodialysis can be helpful in severe cases.

Symptomatic hypermagnesemia is fairly uncommon. It occurs most commonly in patients with renal failure after ingestion of Mg-containing drugs, such as antacids or purgatives.

Symptoms and signs include hyporeflexia, hypotension, respiratory depression, and cardiac arrest.

Diagnosis

Serum Mg concentrations > 2.1 mEq/L (> 1.05 mmol/L)

At serum Mg concentrations of 5 to 10 mEq/L (2.5 to 5 mmol/L), the ECG shows prolongation of the PR interval, widening of the QRS complex, and increased T-wave amplitude. Deep tendon reflexes disappear as the serum Mg concentration approaches 10 mEq/L (5.0 mmol/L); hypotension, respiratory depression, and narcosis develop with increasing hypermagnesemia. Cardiac arrest may occur when blood Mg concentration is > 12 to 15 mEq/L (6.0 to 7.5 mmol/L).

Treatment

• Ca gluconate

• Diuresis or dialysis

Treatment of severe Mg toxicity consists of circulatory and respiratory support with administration of 10% Ca gluconate 10 to 20 mL IV. Ca gluconate may reverse many of the Mg-induced changes, including respiratory depression. Administration of IV furosemide can increase Mg excretion when renal function is adequate; volume status should be maintained. Hemodialysis may be valuable in severe hypermagnesemia, because a relatively large fraction (about 70%) of blood Mg is not protein bound and thus removable with hemodialysis. When hemodynamic compromise occurs and hemodialysis is impractical, peritoneal dialysis is an option.

Chapter 98. Acid-Base Regulation and Disorders

Introduction

Metabolic processes continually produce acid and, to a lesser degree, base. Hydrogen ion (H^+) is especially reactive; it can attach to negatively charged proteins and, in high concentrations, alter their overall charge, configuration, and function. To maintain cellular function, the body has elaborate mechanisms that maintain blood H^+ concentration within a narrow range—typically 37 to 43 nmol/L (pH 7.43 to 7.37, where pH = -log [H^+]) and ideally 40 nmol/L (pH = 7.40). Disturbances of these mechanisms can have serious clinical consequences.

Acid-base equilibrium is closely tied to fluid and electrolyte balance, and disturbances in one of these systems often affect another. Fluid and electrolytes are discussed in Ch. 97.

Acid-Base Physiology

Most acid comes from carbohydrate and fat metabolism, which generates 15,000 to 20,000 mmol of CO_2 daily. CO_2 is not an acid itself but combines with water (H_2O) in the blood to create carbonic acid (H_2CO_3), which in the presence of the enzyme carbonic anhydrase dissociates into H^+ and HCO_3^-. The H^+ binds with Hb in RBCs and is released with oxygenation in the alveoli, at which time the reaction is reversed, creating H_2O and CO_2, which is exhaled in each breath.

Lesser amounts of organic acid derive from the following:

• Incomplete metabolism of glucose and fatty acids into lactic acid and ketoacids

• Metabolism of sulfur-containing amino acids (cysteine, methionine) into sulfuric acid

• Metabolism of cationic amino acids (arginine, lysine)

• Hydrolysis of dietary phosphate

This "fixed" or "metabolic" acid load cannot be exhaled and therefore must be neutralized or excreted.

Most base comes from metabolism of anionic amino acids (glutamate and aspartate) and from oxidation and consumption of organic anions such as lactate and citrate, which produce HCO_3^-.

Acid-Base Balance

Acid-base balance is maintained by chemical buffering and by pulmonary and renal elimination.

Chemical buffering: Chemical buffers are solutions that resist changes in pH. Intracellular and extracellular buffers provide an immediate response to acid-base disturbances. Bone also plays an important buffering role. A buffer is made up of a weak acid and its conjugate base. The conjugate base can accept H^+ and the weak acid can relinquish it thereby minimizing changes in free H^+ concentration.

The most important extracellular buffer is the HCO_3^-/CO_2 system, described by the equation:

$$H^+ + HCO_3^- \Leftrightarrow H_2CO_3 \Leftrightarrow CO_2 + H_2O$$

An increase in H^+ drives the equation to the right and generates CO_2. This important buffer system is highly regulated; CO_2 concentrations can be finely controlled by alveolar ventilation, and H^+ and HCO_3^-

concentrations can be finely regulated by renal excretion.

The relationship between HCO_3^- and CO_2 in the system can be described by the Kassirer-Bleich equation, derived from the Henderson-Hasselbalch equation:

$$H^+ = 24 \times PCO_2/HCO_3^-$$

This equation illustrates that acid-base balance depends on the ratio of PCO_2 and HCO_3^-, not on the absolute value of either one alone. With this formula, any 2 values (usually H^+ and PCO_2) can be used to calculate the other (usually HCO_3^-).

Other important physiologic buffers include intracellular organic and inorganic phosphates and proteins, including Hb in RBCs. Less important are extracellular phosphate and plasma proteins. Bone becomes an important buffer after consumption of extracellular HCO_3^-. Bone initially releases sodium carbonate ($NaHCO_3$) and potassium carbonate ($KHCO_3$) in exchange for H^+. With prolonged acid loads, bone releases calcium carbonate ($CaCO_3$) and calcium phosphate ($CaPO_4$). Long-standing acidemia therefore contributes to bone demineralization and osteoporosis.

Pulmonary regulation: CO_2 concentration is finely regulated by changes in tidal volume and respiratory rate (minute ventilation). A decrease in pH is sensed by arterial chemoreceptors and leads to increases in tidal volume or respiratory rate; CO_2 is exhaled and blood pH increases. In contrast to chemical buffering, which is immediate, pulmonary regulation occurs over minutes to hours. It is about 50 to 75% effective; it does not completely normalize pH.

Renal regulation: The kidneys control pH by adjusting the amount of HCO_3^- that is reabsorbed and the amount of H^+ that is excreted; increase in HCO_3^- is equivalent to removing free H^+. Changes in renal acid-base handling occur hours to days after changes in acid-base status.

HCO_3^- reabsorption occurs mostly in the proximal tubule and, to a lesser degree, in the collecting tubule. H_2O within the tubular cell dissociates into H^+ and hydroxide (OH^-); in the presence of carbonic anhydrase, the OH^- combines with CO_2 to form HCO_3^-, which is transported back into the peritubular capillary, while the H^+ is secreted into the tubular lumen and joins with freely filtered HCO_3^- to form CO_2 and H_2O, which are also reabsorbed. Thus, reabsorbed HCO_3^- ions are newly generated and not the same as those that were filtered. Decreases in effective circulating volume (such as occur with diuretic therapy) increase HCO_3^- reabsorption, while increases in parathyroid hormone in response to an acid load decrease HCO_3^- reabsorption. Also, increased PCO_2 leads to increased HCO_3^- reabsorption, while Cl^- depletion (typically from volume depletion) leads to increased Na^+ reabsorption and HCO_3^- generation by the proximal tubule.

Acid is actively excreted into the proximal and distal tubules where it combines with urinary buffers —primarily freely filtered HPO_4^{-2}, creatinine, uric acid, and ammonia—to be transported outside the body. The ammonia buffering system is especially important because other buffers are filtered in fixed concentrations and can be depleted by high acid loads; by contrast, tubular cells actively regulate ammonia production in response to changes in acid load. Arterial pH is the main determinant of acid secretion, but excretion is also influenced by K^+, Cl^-, and aldosterone levels. Intracellular K^+ concentration and H^+ secretion are reciprocally related; K^+ depletion causes increased H^+ secretion and hence metabolic alkalosis.

Acid-Base Disorders

Acid-base disorders are changes in arterial PCO_2, serum HCO_3^-, and serum pH.

• Acidemia is serum pH < 7.35.

• Alkalemia is serum pH > 7.45.

• Acidosis refers to physiologic processes that cause acid accumulation or alkali loss.

• Alkalosis refers to physiologic processes that cause alkali accumulation or acid loss.

Actual changes in pH depend on the degree of physiologic compensation and whether multiple processes are present.

Classification

Primary acid-base disturbances are defined as metabolic or respiratory based on clinical context and whether the primary change in pH is due to an alteration in serum HCO_3^- or in PCO_2.

Metabolic acidosis is serum HCO_3^- < 24 mEq/L. Causes are

• Increased acid production

• Acid ingestion

• Decreased renal acid excretion

• GI or renal HCO_3^- loss

Metabolic alkalosis is serum HCO_3^- > 24 mEq/L. Causes are

• Acid loss

• HCO_3^- retention

Respiratory acidosis is PCO_2 > 40 mm Hg (hypercapnia). Cause is

• Decrease in minute ventilation (hypoventilation)

Respiratory alkalosis is PCO_2 < 40 mm Hg (hypocapnia). Cause is

• Increase in minute ventilation (hyperventilation)

Whenever an acid-base disorder is present, compensatory mechanisms begin to correct the pH (see Table 98-1). Compensation cannot return pH completely to normal and never overshoots.

[**Table 98-1.** Primary Changes and Compensations in Simple Acid-Base Disorders]

[
Table 98-2. Clinical Consequences of Acid-Base Disorders]

A simple acid-base disorder is a single acid-base disturbance with its accompanying compensatory response.

Mixed acid-base disorders comprise 2 or more primary disturbances.

Symptoms and Signs

Compensated or mild acid-base disorders cause few symptoms or signs. Severe, uncompensated disorders have multiple cardiovascular, respiratory, neurologic, and metabolic consequences (see Table 98-2 and Fig. 189-4 on p. 1857).

Diagnosis

• ABG

• Serum electrolytes

• Anion gap calculated

• If metabolic acidosis is present, delta gap calculated and Winter's formula applied

• Search for compensatory changes

Evaluation is with ABG and serum electrolytes. The ABG directly measures arterial pH and PCO_2. HCO_3^- levels on ABG are calculated using the Henderson-Hasselbalch equation; levels on serum chemistry panels are directly measured and are more accurate. Acid-base balance is generally most accurately assessed with measurement of pH and pCO_2 on arterial blood. In cases of circulatory failure or during cardiopulmonary resuscitation, measurements on venous blood may more accurately reflect conditions at the tissue level and may be a more useful guide to bicarbonate administration and adequacy of ventilation.

The pH establishes the primary process (acidosis or alkalosis), although it moves toward the normal range with compensation. Changes in PCO_2 reflect the respiratory component, and changes in HCO_3^- reflect the metabolic component. However, several calculations may be required to determine whether changes in PCO_2 and HCO_3^- are primary or compensatory and whether a mixed disorder is present; in mixed disorders, values may be deceptively normal. Interpretation must also consider clinical conditions (eg, chronic lung disease, renal failure, drug overdose).

Sidebar 98-1 The Anion Gap

The anion gap is defined as plasma Na concentration minus the sum of Cl^- and HCO_3^- concentrations; $Na^+ - (Cl^- + HCO_3^-)$. The term "gap" is misleading, because the law of electroneutrality requires the same number of positive and negative charges in an open system; the gap appears on laboratory testing because certain cations (+) and anions (-) are not measured on routine laboratory chemistry panels. Thus

$$Na^+ + \text{unmeasured cations (UC)} = Cl^- + HCO_3^- + \text{unmeasured anions (UA)}$$

and

$$\text{the anion gap, } Na^+ - (Cl^- + HCO_3^-) = UA - UC$$

The predominant unmeasured anions are PO_4^{3-}, sulfate (SO_4^-), various negatively charged proteins, and some organic acids, accounting for 20 to 24 mEq/L. The predominant unmeasured extracellular cations are K^+, Ca^{++}, and Mg^{++} and account for about 11 mEq/L. Thus the typical anion gap is 23 - 11 = 12 mEq/L. The anion gap can be affected by increases or decreases in the UC or UA.

Increased anion gap is most commonly caused by metabolic acidosis in which negatively charged acids —mostly ketones, lactate, sulfates, or metabolites of methanol, ethylene glycol, and salicylate—consume (are buffered by) HCO_3^-. Other causes of increased anion gap include hyperalbuminemia and uremia (increased anions) and hypocalcemia or hypomagnesemia (decreased cations).

Decreased anion gap is unrelated to metabolic acidosis but is caused by hypoalbuminemia (decreased anions); hypercalcemia, hypermagnesemia, lithium intoxication, and hypergammaglobulinemia (increased cations); or hyperviscosity or halide (bromide or iodide) intoxication. The effect of low albumin can be accounted for by adjusting the normal range for the anion gap 2.5 mEq/L upward for every 1-g/dL fall in albumin.

Negative anion gap occurs rarely as a laboratory artifact in severe cases of hypernatremia, hyperlipidemia, and bromide intoxication.

The delta gap: The difference between the patient's anion gap and the normal anion gap is termed the delta gap. This amount is considered an HCO_3^- equivalent, because for every unit rise in the anion gap, the HCO_3^- should lower by 1 (by buffering). Thus, if the delta gap is added to the measured HCO_3^-, the result should be in the normal range for HCO_3^-; elevation indicates the additional presence of a metabolic alkalosis.

Example: A vomiting, ill-appearing alcoholic patient has laboratory results showing

Na, 137; K, 3.8; Cl, 90; HCO_3^-, 22; pH, 7.40; PCO_2, 41; PO_2, 85

At first glance, results appear unremarkable. However, calculations show elevation of the anion gap:

137 - (90 + 22) = 25 (normal, 10)

indicating a metabolic acidosis. Respiratory compensation is evaluated by Winter's formula:

Predicted PCO_2 = 1.5 (22) + 8 ± 2
= 41 ± 2

Predicted = measured, so respiratory compensation is appropriate.

Because there is metabolic acidosis, the delta gap is calculated, and the result is added to measured HCO_3^-:

25 - 10 = 15
15 + 22 = 37

The resulting corrected HCO_3^- is above the normal range for HCO_3^-, indicating a primary metabolic alkalosis is also present. Thus, the patient has a mixed acid-base disorder. Using clinical information, one could theorize a metabolic acidosis arising from alcoholic ketoacidosis combined with a metabolic alkalosis from recurrent vomiting with loss of Cl^- and volume.

The anion gap (see Sidebar 98-1) should always be calculated; elevation almost always indicates a metabolic acidosis. A normal anion gap with a low HCO_3^- (eg, < 24 mEq/L) and high serum Cl^- indicates a non-anion gap (hyperchloremic) metabolic acidosis. If metabolic acidosis is present, a delta gap is calculated (see Sidebar 98-1) to identify concomitant metabolic alkalosis, and Winter's formula is applied

to see whether respiratory compensation is appropriate or reflects a 2nd acid-base disorder (predicted $PCO_2 = 1.5 [HCO_3^-] + 8 \pm 2$; if PCO_2 is higher, there is also a primary respiratory acidosis—if lower, respiratory alkalosis).

Respiratory acidosis is suggested by PCO_2 > 40 mm Hg; HCO_3^- should compensate acutely by increasing 3 to 4 mEq/L for each 10-mm Hg rise in PCO_2 sustained for 4 to 12 h (there may be no increase or only 1 to 2 mEq/L, which slowly increases to 3 to 4 mEq/L over days). Greater increase in HCO_3^- implies a primary metabolic alkalosis; lesser increase suggests no time for compensation or coexisting primary metabolic acidosis.

Metabolic alkalosis is suggested by HCO_3^- > 28 mEq/L. The PCO_2 should compensate by increasing about 0.6 to 0.75 mm Hg for each 1 mEq/L increase in HCO_3^- (up to about 55 mm Hg). Greater increase implies concomitant respiratory acidosis; lesser increase, respiratory alkalosis.

Respiratory alkalosis is suggested by PCO_2 < 38 mm Hg. The HCO_3^- should compensate over 4 to 12 h by decreasing 5 mEq/L for every 10-mm Hg decrease in PCO_2. Lesser decrease means there has been no time for compensation or existence of a primary metabolic alkalosis. Greater decrease implies a primary metabolic acidosis.

Nomograms (acid-base maps) are an alternative way to diagnose mixed disorders, allowing for simultaneous plotting of pH, HCO_3^-, and PCO_2.

Metabolic Acidosis

Metabolic acidosis is primary reduction in HCO_3^-, typically with compensatory reduction in PCO_2; pH may be markedly low or slightly subnormal. Metabolic acidoses are categorized as high or normal anion gap based on the presence or absence of unmeasured anions in serum. Causes include accumulation of ketones and lactic acid, renal failure, and drug or toxin ingestion (high anion gap) and GI or renal HCO_3^- loss (normal anion gap). Symptoms and signs in severe cases include nausea and vomiting, lethargy, and hyperpnea. Diagnosis is clinical and with ABG and serum electrolyte measurement. The cause is treated; IV $NaHCO_3$ may be indicated when pH is very low.

Etiology

Metabolic acidosis is acid accumulation due to increased acid production or acid ingestion; decreased acid excretion; or GI or renal HCO_3^- loss. Acidemia (arterial pH < 7.35) results when acid load overwhelms respiratory compensation. Causes are classified by their effect on the anion gap (see Sidebar 98-1 and Table 98-3).

High anion gap acidosis: The most common causes of a high anion gap metabolic acidosis are

- Ketoacidosis,
- Lactic acidosis
- Renal failure
- Toxic ingestions

Ketoacidosis is a common complication of type 1 diabetes mellitus, but it also occurs with chronic

alcoholism, undernutrition, and, to a lesser degree, fasting. In these conditions, the body converts from glucose to free fatty acid (FFA) metabolism; FFAs are converted by the liver into ketoacids, acetoacetic acid, and β-hydroxybutyrate (all unmeasured anions). Ketoacidosis is also a rare manifestation of congenital isovaleric and methylmalonic acidemia.

Lactic acidosis (see p. 861) is the most common cause of metabolic acidosis in hospitalized patients. Lactate accumulation results from a combination of excess formation and decreased utilization of lactate. Excess lactate production occurs during states of anaerobic metabolism. The most serious form occurs during the various types of shock. Decreased utilization generally occurs with hepatocellular dysfunction from decreased liver perfusion or as a part of generalized shock.

Renal failure causes anion gap acidosis by decreased acid excretion and decreased HCO_3^- reabsorption. Accumulation of sulfates, phosphates, urate, and hippurate accounts for the high anion gap.

Toxins may have acidic metabolites or trigger lactic acidosis. Rhabdomyolysis is a rare cause of metabolic acidosis thought to be due to release of protons and anions directly from muscle.

Normal anion gap acidosis: The most common causes of normal anion gap acidosis are

• GI or renal HCO_3^- loss

• Impaired renal acid excretion

Normal anion gap metabolic acidosis is also called hyperchloremic acidosis because the kidneys resorb Cl^- with Na instead of reabsorbing HCO_3^-.

Many GI secretions are rich in HCO_3^- (eg, biliary, pancreatic, and intestinal fluids); loss due to diarrhea, tube drainage, or fistulas can cause acidosis. In ureterosigmoidostomy (insertion of ureters into the sigmoid colon after obstruction or cystectomy), the colon secretes and loses HCO_3^- in exchange for urinary Cl^-

[**Table 98-3.** Causes of Metabolic Acidosis]

and absorbs urinary ammonium, which dissociates into ammonia (NH_3^+) and hydrogen ion (H^+). Ion-exchange resin uncommonly causes HCO_3^- loss by binding HCO_3^-.

The renal tubular acidoses (see p. 2426) either impair H^+ secretion (types 1 and 4) or HCO_3^- absorption (type 2). Impaired acid excretion and a normal anion gap also occur in early renal failure, tubulointerstitial renal disease, and when carbonic anhydrase inhibitors (eg, acetazolamide) are taken.

Symptoms and Signs

Symptoms and signs (see Table 98-2) are primarily those of the cause. Mild acidemia is itself asymptomatic. More severe acidemia (pH < 7.10) may cause nausea, vomiting, and malaise. Symptoms may appear at higher pH if acidosis develops rapidly. The most characteristic sign is hyperpnea (long, deep breaths at a normal rate), reflecting a compensatory increase in alveolar ventilation.

Severe, acute acidemia predisposes to cardiac dysfunction with hypotension and shock, ventricular arrhythmias, and coma. Chronic acidemia causes bone demineralization disorders (eg, rickets, osteomalacia, osteopenia).

Diagnosis

• ABG and serum electrolytes

• Anion gap and delta gap calculated

• Winter's formula for calculating compensatory changes

• Testing for cause

Recognition of metabolic acidosis and appropriate respiratory compensation are discussed on p. 857. Determining the cause of metabolic acidosis begins with the anion gap.

The cause of an elevated anion gap may be clinically obvious (eg, hypovolemic shock, missed hemodialysis), but if not, blood testing should include glucose, BUN, creatinine, lactate, and tests for possible toxins. Salicylate levels can be measured in most laboratories, but methanol and ethylene glycol frequently cannot; their presence may be suggested by presence of an osmolar gap. Calculated serum osmolarity (2 [Na] + [glucose]/18 + BUN/2.8 + blood alcohol/5) is subtracted from measured osmolarity. A difference > 10 implies the presence of an osmotically active substance, which in the case of a high anion gap acidosis is methanol or ethylene glycol. Although ingestion of ethanol may cause an osmolar gap and a mild acidosis, it should never be considered the cause of a significant metabolic acidosis.

If the anion gap is normal and no cause is obvious (eg, marked diarrhea), urinary electrolytes are measured and the urinary anion gap is calculated as [Na] + [K] - [Cl]. A normal urinary anion gap (including in patients with GI losses) is 30 to 50 mEq/L; an elevation suggests renal HCO_3^- loss (for evaluation of renal tubular acidosis, see p. 2427). In addition, when metabolic acidosis is present, a delta gap is calculated (see Sidebar 98-1) to identify concomitant metabolic alkalosis, and Winter's formula (see p. 858) is applied to see whether respiratory compensation is appropriate or reflects a 2nd acid-base disorder.

Treatment

• Cause treated

• $NaHCO_3$ rarely indicated

Treatment is directed at the underlying cause. Hemodialysis is required for renal failure and sometimes for ethylene glycol, methanol, and salicylate poisoning.

Treatment of acidemia with $NaHCO_3$ is clearly indicated only in certain circumstances and is probably deleterious in others. When metabolic acidosis results from loss of HCO_3^- or accumulation of inorganic acids (ie, normal anion gap acidosis), HCO_3^- therapy is generally safe and appropriate. However, when acidosis results from organic acid accumulation (ie, high anion gap acidosis), HCO_3^- therapy is controversial; it does not clearly decrease mortality in these conditions, and there are several possible risks. With treatment of the underlying condition, lactate and ketoacids are metabolized back to HCO_3^-; exogenous HCO_3^- loading may therefore cause an "overshoot" metabolic alkalosis. In any condition, HCO_3^- may also cause Na and volume overload, hypokalemia, and, by inhibiting respiratory drive, hypercapnia. Furthermore, because HCO_3^- does not diffuse across cell membranes, intracellular acidosis is not corrected and may paradoxically worsen because some of the added HCO_3^- is converted to CO_2, which does cross into the cell and is hydrolyzed to H^+ and HCO_3^-.

Despite these and other controversies, most experts still recommend HCO_3^- IV for severe metabolic acidosis (pH < 7.00), with a target pH of 7.20.

Treatment requires 2 calculations. The first is the level to which HCO_3^- must be raised, calculated by the

Kassirer-Bleich equation, using a value for $[H^+]$ of 63 nmol/L at a pH of 7.2:

$63 = 24 \times PCO_2/HCO_3^-$

or

$\text{desired } HCO_3^- = 0.38 \times PCO_2$

The amount of HCO_3^- needed to achieve that level is

$NaHCO_3 \text{ required (mEq)} = (\text{desired } [HCO_3^-] - \text{observed } [HCO_3^-]) \times 0.4 \times \text{body weight (kg)}$

This amount of $NaHCO_3$ is given over several hours. Serum pH and HCO_3^- levels can be checked 30 min to 1 h after administration, which allows for equilibration with extravascular HCO_3^-.

Alternatives to $NaHCO_3$ include

- Tromethamine, an amino alcohol that buffers both metabolic (H^+) and respiratory (carbonic acid [H_2CO_3]) acid
- Carbicarb, an equimolar mixture of $NaHCO_3$ and carbonate (the latter consumes CO_2 and generates HCO_3^-)
- Dichloroacetate, which enhances oxidation of lactate

These alternatives are all of unproven benefit and cause complications of their own.

K^+ depletion, common in metabolic acidosis, should be identified through frequent serum K^+ monitoring and treated as needed with oral or parenteral KCl.

Lactic Acidosis

Lactic acidosis results from overproduction of lactate, decreased metabolism of lactate, or both.

Lactate is a normal byproduct of glucose and amino acid metabolism. The most serious form of lactic acidosis, type A, occurs when lactic acid is overproduced in ischemic tissue to generate ATP during O_2 deficit. Overproduction typically occurs during tissue hypoperfusion in hypovolemic, cardiac, or septic shock and is worsened by decreased lactate metabolism in the poorly perfused liver. It may also occur with primary hypoxia due to lung disease and with various hemoglobinopathies.

Type B lactic acidosis occurs in states of normal global tissue perfusion (and hence ATP production) and is less ominous. Lactate production may be increased from local relative hypoxia as with vigorous muscle use (eg, exertion, seizures, hypothermic shivering) and with cancer and ingestion of certain drugs or toxins (see Table 98-3). Drugs include the nucleoside reverse transcriptase inhibitors and the biguanides phenformin and, less so, metformin; although phenformin has been removed from the market in most of the world, it is still available from China (including as a component of some Chinese proprietary medicines). Metabolism may be decreased due to hepatic insufficiency or thiamin deficiency.

D-Lactic acidosis is an unusual form of lactic acidosis in which D-lactic acid, the product of bacterial carbohydrate metabolism in the colon of patients with jejunoileal bypass or intestinal resection, is systemically absorbed. It persists in circulation because human lactate dehydrogenase can metabolize only L-lactate.

Findings in and treatment of types A and B lactic acidosis are as for other metabolic acidoses. In D-lactic acidosis, the anion gap is lower than expected for the decrease in HCO_3^-, and there may be a urinary osmolar gap (difference between calculated and measured urine osmolarity). Treatment is IV fluids, restriction of carbohydrates, and sometimes antibiotics (eg, metronidazole).

Metabolic Alkalosis

Metabolic alkalosis is primary increase in HCO_3^- with or without compensatory increase in PCO_2; pH may be high or nearly normal. Common causes include prolonged vomiting, hypovolemia, diuretic use, and hypokalemia. Renal impairment of HCO_3^- excretion must be present to sustain alkalosis. Symptoms and signs in severe cases include headache, lethargy, and tetany. Diagnosis is clinical and with ABG and serum electrolyte measurement. The underlying cause is treated; oral or IV acetazolamide or HCl is sometimes indicated.

Etiology

Metabolic alkalosis is HCO_3^- accumulation due to acid loss, alkali administration, intracellular shift of hydrogen ion (H^+—as occurs in hypokalemia), or HCO_3^- retention. Regardless of initial cause, persistence of metabolic alkalosis indicates that the kidneys have increased their HCO_3^- reabsorption, because HCO_3^- is normally freely filtered by the kidneys and hence excreted. Volume depletion and hypokalemia are the most common stimuli for increased HCO_3^- reabsorption, but any condition that elevates aldosterone or mineralocorticoids (which enhance Na reabsorption and K and H^+ excretion) can elevate HCO_3^-. Thus, hypokalemia is both a cause and a frequent consequence of metabolic alkalosis. Causes are listed; the most common are volume depletion (particularly when involving loss of gastric acid and Cl from recurrent vomiting or nasogastric suction) and diuretic use (see Table 98-4).

Metabolic alkalosis involving loss or excess secretion of Cl is termed Cl-responsive, because it typically corrects with IV administration of NaCl-containing fluid. Cl-unresponsive metabolic alkalosis does not, and it typically involves severe Mg or K deficiency or mineralocorticoid excess. The 2 forms can coexist, eg, in patients with volume overload made hypokalemic from high-dose diuretics.

Symptoms and Signs

Symptoms and signs of mild alkalemia are usually related to the underlying disorder. More severe alkalemia increases protein binding of ionized Ca^{++}, leading to hypocalcemia and subsequent headache, lethargy, and neuromuscular excitability, sometimes with delirium, tetany, and seizures. Alkalemia also lowers threshold for anginal symptoms and arrhythmias. Concomitant hypokalemia may cause weakness.

Diagnosis

• ABG and sercum electrolytes

• Diagnosis of cause usually clinical

• Sometimes measurement of urinary Cl^- and K^+

Recognition of metabolic alkalosis and appropriate respiratory compensation is discussed on p. 857 and requires ABG and measurement of serum electrolytes (including Ca and Mg).

Common causes can often be determined by history and physical examination. If history is unrevealing and renal function is normal, urinary Cl^- and K^+ concentrations are measured (values are not diagnostic

in renal insufficiency). Urinary Cl < 20 mEq/L indicates significant renal Cl^- reabsorption and hence a Cl-responsive cause (see Table 98-4). Urinary Cl > 20 mEq/L suggests a Cl-unresponsive form.

Urinary K and presence or absence of hypertension help differentiate Cl-unresponsive alkaloses. Urinary K < 30 mEq/day signifies hypokalemia or laxative misuse. Urinary K > 30 mEq/day without hypertension suggests diuretic abuse or Bartter or Gitelman's syndrome. Urinary K > 30 mEq/day with hypertension requires evaluation for hyperaldosteronism, mineralocorticoid excess, and

[**Table 98-4.** Causes of Metabolic Alkalosis]

renovascular disease. Tests typically include plasma renin activity and aldosterone and cortisol levels (see pp. 797 and 800).

Treatment

• Cause treated

• IV 0.9% saline solution for Cl-responsive metabolic alkalosis

Underlying conditions are treated, with particular attention paid to correction of hypovolemia and hypokalemia.

Patients with Cl-responsive metabolic alkalosis are given 0.9% saline solution IV; infusion rate is typically 50 to 100 mL/h greater than urinary and other sensible and insensible fluid losses until urinary Cl rises to > 25 mEq/L and urinary pH normalizes after an initial rise from bicarbonaturia. Patients with Cl-unresponsive metabolic alkalosis rarely benefit from rehydration alone.

Patients with severe metabolic alkalosis (eg, pH > 7.6) sometimes require more urgent correction of serum pH. Hemofiltration or hemodialysis is an option, particularly if volume overload and renal dysfunction are present. Acetazolamide 250 to 375 mg po or IV once/day or bid increases HCO_3^- excretion but may also accelerate urinary losses of K^+ and phosphate (PO_4^-); volume-overloaded patients with diuretic-induced metabolic alkalosis and those with posthypercapnic metabolic alkalosis may especially benefit.

Hydrochloric acid in a 0.1 to 0.2 normal solution IV is safe and effective but must be given through a central catheter because it is hyperosmotic and scleroses peripheral veins. Dosage is 0.1 to 0.2 mmol/kg/h. Frequent monitoring of ABG and electrolytes is needed.

Respiratory Acidosis

Respiratory acidosis is primary increase in PCO_2 with or without compensatory increase in HCO_3^-; pH is usually low but may be near normal. Cause is a decrease in respiratory rate, volume (hypoventilation), or both due to CNS, pulmonary, or iatrogenic conditions. Respiratory acidosis can be acute or chronic; the chronic form is asymptomatic, but the acute, or worsening, form causes headache, confusion, and drowsiness. Signs include tremor, myoclonic jerks, and asterixis. Diagnosis is clinical and with ABG and serum electrolyte measurements. The cause is treated; O_2 and mechanical ventilation are often required.

Respiratory acidosis is CO_2 accumulation (hypercapnia) due to a decrease in respiratory rate, respiratory volume (hypoventilation), or both. Causes of hypoventilation (discussed under Ventilatory Failure on p. 2288) include

• Conditions that impair CNS respiratory drive

• Conditions that impair neuromuscular transmission and other conditions that cause muscular weakness

• Obstructive, restrictive, and parenchymal pulmonary disorders

Hypoxia typically accompanies hypoventilation.

Respiratory acidosis may be acute or chronic. Distinction is based on the degree of metabolic compensation; CO_2 is initially buffered inefficiently, but over 3 to 5 days the kidneys increase HCO_3^- reabsorption significantly.

Symptoms and Signs

Symptoms and signs depend on the rate and degree of PCO_2 increase. CO_2 rapidly diffuses across the blood-brain barrier. Symptoms and signs are a result of high CNS CO_2 concentrations (low CNS pH) and any accompanying hypoxemia.

Acute (or acutely worsening chronic) respiratory acidosis causes headache, confusion, anxiety, drowsiness, and stupor (CO_2 narcosis). Slowly developing, stable respiratory acidosis (as in COPD) may be well tolerated, but patients may have memory loss, sleep disturbances, excessive daytime sleepiness, and personality changes. Signs include gait disturbance, tremor, blunted deep tendon reflexes, myoclonic jerks, asterixis, and papilledema.

Diagnosis

• ABG and serum electrolytes

• Diagnosis of cause usually clinical

Recognition of respiratory acidosis and appropriate renal compensation (see p. 857) requires ABG and measurement of serum electrolytes. Causes are usually obvious from history and examination. Calculation of the alveolar-arterial (A-a) O_2 gradient (inspired PO_2 - [arterial PO_2 + 5/4 arterial PCO_2]) can help distinguish pulmonary from extrapulmonary disease; a normal gradient essentially excludes pulmonary disorders.

Treatment

• Adequate ventilation

• $NaHCO_3$ almost always contraindicated

Treatment is provision of adequate ventilation by either endotracheal intubation or noninvasive positive pressure ventilation (for specific indications and procedures, see Ch. 225). Adequate ventilation is all that is needed to correct respiratory acidosis, although chronic hypercapnia generally must be corrected slowly (eg, over several hours or more), because too-rapid PCO_2 lowering can cause a posthypercapnic "overshoot" alkalosis when the underlying compensatory hyperbicarbonatemia becomes unmasked; the abrupt rise in CNS pH that results can lead to seizures and death. Any K^+ and Cl^- deficits are corrected.

$NaHCO_3$ is almost always contraindicated, because HCO_3^- can be converted to PCO_2 in serum but crosses the blood-brain barrier slowly, thus increasing serum pH without affecting CNS pH. One exception may be in cases of severe bronchospasm, in which HCO_3^- may improve responsiveness of bronchial smooth muscle to β-agonists.

Respiratory Alkalosis

(See also Hyperventilation Syndrome on p. 1836.)

Respiratory alkalosis is a primary decrease in Pco_2 with or without compensatory decrease in

HCO_3^-; pH may be high or near normal. Cause is an increase in respiratory rate or volume (hyperventilation) or both. Respiratory alkalosis can be acute or chronic. The chronic form is asymptomatic, but the acute form causes light-headedness, confusion, paresthesias, cramps, and syncope. Signs include hyperpnea or tachypnea and carpopedal spasms. Diagnosis is clinical and with ABG and serum electrolyte measurements. Treatment is directed at the cause.

Etiology

Respiratory alkalosis is a primary decrease in PCO_2 (hypocapnia) due to an increase in respiratory rate or volume (hyperventilation) or both. Ventilation increase occurs most often as a physiologic response to hypoxia, metabolic acidosis, and increased metabolic demands (eg, fever) and, as such, is present in many serious conditions. In addition, pain and anxiety and some CNS disorders can increase respirations without a physiologic need.

Pathophysiology

Respiratory alkalosis can be acute or chronic. Distinction is based on the degree of metabolic compensation. Excess HCO_3^- is buffered by extracellular hydrogen ion (H^+) within minutes, but more significant compensation occurs over 2 to 3 days as the kidneys decrease H^+ excretion.

Pseudorespiratory alkalosis: Pseudorespiratory alkalosis is low arterial PCO_2 and high pH in mechanically ventilated patients with severe metabolic acidosis due to poor systemic perfusion (eg, cardiogenic shock, during CPR). Pseudorespiratory alkalosis occurs when mechanical ventilation (often hyperventilation) eliminates larger-than-normal amounts of alveolar CO_2. Exhalation of large amounts of CO_2 causes respiratory alkalosis in arterial blood (hence on ABG measurements), but poor systemic perfusion and cellular ischemia cause cellular acidosis, leading to acidosis of venous blood. Diagnosis is by demonstration of marked arteriovenous differences in PCO_2 and pH and by elevated lactate levels; treatment is improvement of systemic hemodynamics.

Symptoms and Signs

Symptoms and signs depend on the rate and degree of fall in PCO_2. Acute respiratory alkalosis causes light-headedness, confusion, peripheral and circumoral paresthesias, cramps, and syncope. Mechanism is thought to be change in cerebral blood flow and pH. Tachypnea or hyperpnea is often the only sign; carpopedal spasm may occur in severe cases. Chronic respiratory alkalosis is usually asymptomatic and has no distinctive signs.

Diagnosis

• ABG and serum electrolytes

• If hypoxia present, cause vigorously pursued

Recognition of respiratory alkalosis and appropriate renal compensation (discussed on p. 857) requires ABG and serum electrolyte measurements. Minor hypophosphatemia and hypokalemia due to intracellular shifts and decreased ionized Ca^{++} due to an increase in protein binding may be present.

Presence of hypoxia or an increased alveolar-arterial (A-a) O_2 gradient (inspired PO_2 - [arterial PO_2 + 5/4 arterial PCO_2]) requires search for a cause. Other causes are often apparent on history and examination. However, because pulmonary embolism often manifests without hypoxia (see p. 1908), embolism must be strongly considered in a hyperventilating patient before ascribing the cause to anxiety.

Treatment

Treatment is directed at the underlying cause. Respiratory alkalosis is not life threatening, so no

interventions to lower pH are necessary. Increasing inspired CO_2 through rebreathing (such as from a paper bag) is common practice but may be dangerous in at least some patients with CNS disorders in whom CSF pH may already be below normal.

Chapter 99. Diabetes Mellitus and Disorders of Carbohydrate Metabolism

Introduction

Diabetes mellitus and its complications (diabetic ketoacidosis, nonketotic hyperosmolar syndrome) are the most common disorders of carbohydrate metabolism, but alcoholic ketoacidosis and hypoglycemia are also important.

Diabetes Mellitus

Diabetes mellitus (DM) is impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia. Early symptoms are related to hyperglycemia and include polydipsia, polyphagia, and polyuria. Later complications include vascular disease, peripheral neuropathy, and predisposition to infection. Diagnosis is by measuring plasma glucose. Treatment is diet, exercise, and drugs that reduce glucose levels, including insulin and oral antihyperglycemic drugs. Prognosis varies with degree of glucose control.

There are 2 main categories of DM—type 1 and type 2, which can be distinguished by a combination of features (see Table 99-1). Terms that describe the age of onset (juvenile or adult) or type of treatment (insulin- or non-insulin-dependent) are no longer accurate because of overlap in age groups and treatments between disease types.

Impaired glucose regulation (impaired glucose tolerance, or impaired fasting glucose—see Table 99-2) is an intermediate, possibly transitional, state between normal glucose metabolism and DM that becomes common with age. It is a significant risk factor for DM and may be present for many years before onset of DM. It is associated with an increased

[**Table 99-1.** General Characteristics of Types 1 and 2 Diabetes Mellitus]

[**Table 99-2.** Diagnostic Criteria for Diabetes Mellitus and Impaired Glucose Regulation]

risk of cardiovascular disease, but typical diabetic microvascular complications generally do not develop.

Etiology

Type 1: In Type 1 DM (previously called juvenile-onset or insulin-dependent), insulin production is absent because of autoimmune pancreatic β-cell destruction possibly triggered by an environmental exposure in genetically susceptible people. Destruction progresses subclinically over months or years until β-cell mass decreases to the point that insulin concentrations are no longer adequate to control plasma glucose levels. Type 1 DM generally develops in childhood or adolescence and until recently was the most common form diagnosed before age 30; however, it can also develop in adults (latent autoimmune diabetes of adulthood, which often initially seems to be type 2 DM). Some cases of type 1 DM, particularly in nonwhite populations, do not seem to be autoimmune in nature and are considered idiopathic. Type 1 accounts for < 10% of all cases of DM.

The pathogenesis of the autoimmune β-cell destruction involves incompletely understood interactions between susceptibility genes, autoantigens, and environmental factors. Susceptibility genes include those within the major histocompatibility complex (MHC)—especially HLA-DR3, DQB1*0201 and HLA-DR4, DQB1*0302, which are present in > 90% of patients with type 1 DM—and those outside the MHC, which seem to regulate insulin production and processing and confer risk of DM in concert with MHC genes. Susceptibility genes are more common among some populations than among others and explain the higher prevalence of type 1 DM among some ethnic groups (Scandinavians, Sardinians).

Autoantigens include glutamic acid decarboxylase, insulin, insulinoma-associated protein, and other proteins in β cells. It is thought that these proteins are exposed or released during normal β-cell turnover or β-cell injury (eg, due to infection), activating a cell-mediated immune response resulting in β-cell destruction (insulitis). Glucagon-secreting α cells remain unharmed. Antibodies to autoantigens, which

can be detected in serum, seem to be a response to (not a cause of) β-cell destruction.

Several viruses (including coxsackievirus, rubella virus, cytomegalovirus, Epstein-Barr virus, and retroviruses) have been linked to the onset of type 1 DM. Viruses may directly infect and destroy β cells, or they may cause β-cell destruction indirectly by exposing autoantigens, activating autoreactive lymphocytes, mimicking molecular sequences of autoantigens that stimulate an immune response (molecular mimicry), or other mechanisms.

Diet may also be a factor. Exposure of infants to dairy products (especially cow's milk and the milk protein β casein), high nitrates in drinking water, and low vitamin D consumption have been linked to increased risk of type 1 DM. Early (< 4 mo) or late (> 7 mo) exposure to gluten and cereals increases islet cell autoantibody production. Mechanisms for these associations are unclear.

Type 2: In type 2 DM (previously called adult-onset or non-insulin-dependent), insulin secretion is inadequate. Often insulin levels are very high, especially early in the disease, but peripheral insulin resistance and increased hepatic production of glucose make insulin levels inadequate to normalize plasma glucose levels. Insulin production then falls, further exacerbating hyperglycemia. The disease generally develops in adults and becomes more common with age. Plasma glucose levels reach higher levels after eating in older than in younger adults, especially after high carbohydrate loads, and take longer to return to normal, in part because of increased accumulation of visceral and abdominal fat and decreased muscle mass.

Type 2 DM is becoming increasingly common among children as childhood obesity has become epidemic: 40 to 50% of new-onset DM in children is now type 2. Over 90% of adults with DM have type 2 disease. There are clear genetic determinants, as evidenced by the high prevalence of the disease within ethnic groups (especially American Indians, Hispanics, and Asians) and in relatives of people with the disease. Although several genetic polymorphisms have been identified, no gene responsible for the most common forms of type 2 DM has been identified.

Pathogenesis is complex and incompletely understood. Hyperglycemia develops when insulin secretion can no longer compensate for insulin resistance. Although insulin resistance is characteristic in people with type 2 DM and those at risk for it, evidence also exists for β-cell dysfunction and impaired insulin secretion, including impaired first-phase insulin secretion in response to IV glucose infusion, a loss of normally pulsatile insulin secretion, an increase in proinsulin secretion signaling impaired insulin processing, and an accumulation of islet amyloid polypeptide (a protein normally secreted with insulin). Hyperglycemia itself may impair insulin secretion, because high glucose levels desensitize β cells, cause β-cell dysfunction (glucose toxicity), or both. These changes typically take years to develop in the presence of insulin resistance.

Obesity and weight gain are important determinants of insulin resistance in type 2 DM. They have some genetic determinants but also reflect diet, exercise, and lifestyle. Adipose tissue increases plasma levels of free fatty acids that may impair insulin-stimulated glucose transport and muscle glycogen synthase activity. Adipose tissue also seems to function as an endocrine organ, releasing multiple factors (adipocytokines) that favorably (adiponectin) and adversely (tumor necrosis factor-α, IL-6, leptin, resistin) influence glucose metabolism. Intrauterine growth restriction and low birth weight have also been associated with insulin resistance in later life and may reflect prenatal environmental influences on glucose metabolism.

Miscellaneous types: Miscellaneous causes of DM that account for a small proportion of cases include genetic defects affecting β-cell function, insulin action, and mitochondrial DNA (eg, maturity-onset diabetes of youth); pancreatic diseases (eg, cystic fibrosis, pancreatitis, hemochromatosis); endocrinopathies (eg, Cushing's syndrome, acromegaly); toxins (eg, the rodenticide pyriminyl [Vacor]); and drug-induced diabetes, most notably from glucocorticoids, β-blockers, protease inhibitors, and therapeutic doses of niacin. Pregnancy causes some insulin resistance in all women, but only a few develop gestational DM (see p. 2638).

Symptoms and Signs

The most common symptoms of DM are those of hyperglycemia: an osmotic diuresis caused by glycosuria leading to urinary frequency, polyuria, and polydipsia that may progress to orthostatic hypotension and dehydration. Severe dehydration causes weakness, fatigue, and mental status changes. Symptoms may come and go as plasma glucose levels fluctuate. Polyphagia may accompany symptoms of hyperglycemia but is not typically a primary patient concern. Hyperglycemia can also cause weight loss, nausea and vomiting, and blurred vision, and it may predispose to bacterial or fungal infections.

Patients with type 1 DM typically present with symptomatic hyperglycemia and sometimes with diabetic ketoacidosis (DKA—see p. 883). Some patients experience a long but transient phase of near-normal glucose levels after acute onset of the disease (honeymoon phase) due to partial recovery of insulin secretion.

Patients with type 2 DM may present with symptomatic hyperglycemia but are often asymptomatic, and their condition is detected only on routine testing. In some patients, initial symptoms are those of diabetic complications, suggesting that the disease has been present for some time. In some patients, hyperosmotic coma occurs initially, especially during a period of stress or when glucose metabolism is further impaired by drugs, such as corticosteroids.

Complications

Years of poorly controlled hyperglycemia lead to multiple, primarily vascular complications that affect small (microvascular) vessels, large (macrovascular) vessels, or both. The mechanisms by which vascular disease develops include glycosylation of serum and tissue proteins with formation of advanced glycation end products; superoxide production; activation of protein kinase C, a signaling molecule that increases vascular permeability and causes endothelial dysfunction; accelerated hexosamine biosynthetic and polyol pathways leading to sorbitol accumulation within tissues; hypertension and dyslipidemias that commonly accompany DM; arterial microthromboses; and proinflammatory and prothrombotic effects of hyperglycemia and hyperinsulinemia that impair vascular autoregulation. Immune dysfunction is another major complication and develops from the direct effects of hyperglycemia on cellular immunity.

Microvascular disease underlies the 3 most common and devastating manifestations of DM:

• Retinopathy

• Nephropathy

• Neuropathy

Microvascular disease may also impair skin healing, so that even minor breaks in skin integrity can develop into deeper ulcers and easily become infected, particularly in the lower extremities. Intensive control of plasma glucose can prevent many of these complications but may not reverse them once established.

Diabetic retinopathy: Diabetic retinopathy is the most common cause of adult blindness in the US (see also p. 615). It is characterized initially by retinal capillary microaneurysms and later by macular edema and neovascularization (see Plate 23). There are no early symptoms or signs, but focal blurring, vitreous or retinal detachment, and partial or total vision loss eventually develop; rate of progression is highly variable. Diagnosis is by retinal examination. Treatment is argon laser photocoagulation or vitrectomy. Strict glycemic control and early detection and treatment are critical to preventing vision loss.

Diabetic nephropathy: Diabetic nephropathy (see also p. 2401) is a leading cause of chronic renal failure in the US. It is characterized by thickening of the glomerular basement membrane, mesangial expansion, and glomerular sclerosis. These changes cause glomerular hypertension and progressive decline in GFR. Systemic hypertension may accelerate progression. The disease is usually asymptomatic until nephrotic syndrome or renal failure develops.

Diagnosis is by detection of urinary albumin. A urine dipstick positive for protein signifies albumin

excretion > 300 mg/day and advanced diabetic nephropathy (or an improperly collected or stored specimen). If the dipstick is negative for protein, the albumin:creatinine ratio on a spot urine specimen or urinary albumin in a 24-h collection should be measured. A ratio > 30 mg/g or an albumin concentration 30 to 300 mg/24 h signifies microalbuminuria and early diabetic nephropathy.

Treatment is rigorous glycemic control combined with BP control. An ACE inhibitor, an angiotensin II receptor blocker, or both should be used to treat hypertension at the earliest sign of microalbuminuria or even before, because these drugs lower intraglomerular BP and thus have renoprotective effects.

Diabetic neuropathy: Diabetic neuropathy is the result of nerve ischemia due to microvascular disease, direct effects of hyperglycemia on neurons, and intracellular metabolic changes that impair nerve function. There are multiple types, including

• Symmetric polyneuropathy (with small-and large-fiber variants)

• Autonomic neuropathy

• Radiculopathy

• Cranial neuropathy

• Mononeuropathy

Symmetric polyneuropathy is most common and affects the distal feet and hands (stocking-glove distribution); it manifests as paresthesias, dysesthesias, or a painless loss of sense of touch, vibration, proprioception, or temperature. In the lower extremities, these symptoms can lead to blunted perception of foot trauma due to ill-fitting shoes and abnormal weight bearing, which can in turn lead to foot ulceration and infection or to fractures, subluxation, and dislocation or destruction of normal foot architecture (Charcot's joint).

Small-fiber neuropathy is characterized by pain, numbness, and loss of temperature sensation with preserved vibration and position sense. Patients are prone to foot ulceration and neuropathic joint degeneration and have a high incidence of autonomic neuropathy.

Predominant large-fiber neuropathy is characterized by muscle weakness, loss of vibration and position sense, and lack of deep tendon reflexes. Atrophy of intrinsic muscles of the feet and foot drop are common.

Autonomic neuropathy can cause orthostatic hypotension, exercise intolerance, resting tachycardia, dysphagia, nausea and vomiting (due to gastroparesis), constipation and diarrhea (including dumping syndrome), fecal incontinence, urinary retention and incontinence, erectile dysfunction and retrograde ejaculation, and decreased vaginal lubrication.

Radiculopathies most often affect the proximal L2 through L4 nerve roots, causing pain, weakness, and atrophy of the lower extremities (diabetic amyotrophy), or the proximal T_4 through T_{12} nerve roots, causing abdominal pain (thoracic polyradiculopathy).

Cranial neuropathies cause diplopia, ptosis, and anisocoria when they affect the 3rd cranial nerve or motor palsies when they affect the 4th or 6th cranial nerve.

Mononeuropathies cause finger weakness and numbness (median nerve) or foot drop (peroneal nerve). Patients with DM are also prone to nerve compression disorders, such as carpal tunnel syndrome. Mononeuropathies can occur in several places simultaneously (mononeuritis multiplex). All tend to affect older patients predominantly and usually abate spontaneously over months; however, nerve compression disorders do not.

Diagnosis of symmetric polyneuropathy is by detection of sensory deficits and diminished ankle reflexes. Loss of ability to detect the light touch of a nylon monofilament identifies patients at highest risk of foot

ulceration (see Fig. 99-1). Electromyography and nerve conduction studies may be needed for all forms of neuropathy and are sometimes used to exclude other causes of neuropathic symptoms, such as nondiabetic radiculopathy and carpal tunnel syndrome. Strict glycemic control may lessen neuropathy. Treatments for relief of symptoms include topical capsaicin cream, tricyclic antidepressants (eg, imipramine), SNRIs (eg, duloxetine), anticonvulsants (eg, gabapentin, carbamazepine), and mexiletine. Patients with sensory loss should examine their feet daily to detect minor foot trauma and prevent it from progressing to limb-threatening infection.

Macrovascular disease: Large-vessel atherosclerosis is a result of the hyperinsulinemia, dyslipidemias, and hyperglycemia characteristic of DM. Manifestations are

• Angina pectoris and MI

• Transient ischemic attacks and strokes

• Peripheral arterial disease

[**Fig. 99-1.** Diabetic foot screening.]

Diagnosis is by history and examination; the role of screening tests is evolving. Treatment is rigorous control of atherosclerotic risk factors, including normalization of plasma glucose, lipids, and BP, combined with smoking cessation and daily intake of aspirin and ACE inhibitors. In contrast with microvascular disease, intensive control of plasma glucose alone is not an effective preventive measure.

Cardiomyopathy: Diabetic cardiomyopathy is thought to result from many factors, including epicardial atherosclerosis, hypertension and left ventricular hypertrophy, microvascular disease, endothelial and autonomic dysfunction, obesity, and metabolic disturbances. Patients develop heart failure due to impairment in left ventricular systolic and diastolic function and are more likely to develop heart failure after MI.

Infection: Patients with poorly controlled DM are prone to bacterial and fungal infections because of adverse effects of hyperglycemia on granulocyte and T-cell function. Most common are mucocutaneous fungal infections (eg, oral and vaginal candidiasis) and bacterial foot infections (including osteomyelitis), which are typically exacerbated by lower extremity vascular insufficiency and diabetic neuropathy.

Other complications: Diabetic foot complications (skin changes, ulceration, infection, gangrene) are common and are attributable to vascular disease, neuropathy, and relative immunosuppression.

Patients with DM have an increased risk of developing some rheumatologic diseases, including muscle infarction, carpal tunnel syndrome, Dupuytren's contracture, adhesive capsulitis, and sclerodactyly. They may also develop ophthalmologic disease unrelated to diabetic retinopathy (eg, cataracts, glaucoma, corneal abrasions, optic neuropathy); hepatobiliary diseases (eg, nonalcoholic fatty liver disease [steatosis and steatohepatitis], cirrhosis, gallstones); and dermatologic disease (eg, tinea infections, lower-extremity ulcers, diabetic dermopathy, necrobiosis lipoidica diabeticorum, diabetic systemic sclerosis, vitiligo, granuloma annulare, acanthosis nigricans [a sign of insulin resistance]). Depression and dementia are also common.

Diagnosis

• Fasting plasma glucose levels

• Sometimes oral glucose tolerance testing

DM is indicated by typical symptoms and signs and confirmed by measurement of plasma glucose. Measurement after an 8- to 12-h fast (fasting plasma glucose [FPG]) or 2 h after ingestion of a concentrated glucose solution (oral glucose tolerance testing [OGTT]) is best (see Table 99-2). OGTT is more sensitive for diagnosing DM and impaired glucose tolerance but is less convenient and reproducible

than FPG. It is therefore rarely used routinely, except for diagnosing gestational DM (see p. 2638) and for research purposes.

In practice, DM or impaired fasting glucose regulation is often diagnosed using random measures of plasma glucose or of glycosylated Hg (HbA_{1c}). A random glucose value > 200 mg/dL (> 11.1 mmol/L) may be diagnostic, but values can be affected by recent meals and must be confirmed by repeat testing; testing twice may not be necessary in the presence of diabetic symptoms. HbA_{1c} measurements reflect glucose levels over the preceding 2 to 3 mo. HbA_{1c} measurements are now included in the diagnostic criteria for DM: • HbA_{1c} ≥ 6.5% = DM

• HbA_{1c} 5.7 to 6.4% = prediabetes or at risk of DM

However, values may be falsely high or low (see Monitoring on p. 873), and tests must be done in a certified clinical laboratory. HbA_{1c} is also used for monitoring DM control.

Urine glucose measurement, once commonly used, is no longer used for diagnosis or monitoring because it is neither sensitive nor specific.

Screening for disease: Screening for DM should be conducted for people at risk of the disease. Patients with DM are screened for complications.

People at high risk of type 1 DM (eg, siblings and children of people with type 1 DM) can be tested for the presence of islet cell or antiglutamic acid decarboxylase antibodies, which precede onset of clinical disease. However, there are no proven preventive strategies for people at high risk, so such screening is usually reserved for research settings.

Risk factors for type 2 DM include age > 45; obesity; sedentary lifestyle; family history of DM; history of impaired glucose regulation; gestational DM or delivery of a baby > 4.1 kg; history of hypertension or dyslipidemia; polycystic ovary syndrome; and black, Hispanic, or American Indian ethnicity.

Risk of insulin resistance among overweight people (body mass index ≥ 25 kg/m^2) is increased with serum triglycerides ≥ 130 mg/dL (≥ 1.47 mmol/L); triglyceride/high-density lipoprotein (HDL) ratio ≥ 3.0 (≥ 1.8); and insulin ≥ 108 pmol/L. People with these characteristics are at particularly high risk and should be screened for DM with an FPG level at least once every 3 yr as long as plasma glucose measurements are normal and at least annually if results reveal impaired fasting glucose levels (see Table 99-2).

Screening for complications: All patients with type 1 DM should begin screening for diabetic complications 5 yr after diagnosis. For patients with type 2 DM, screening begins at diagnosis. Typical screening for complications includes

• Foot examination

• Funduscopic examination

• Urine testing for proteinuria and microalbuminuria

• Measurement of serum creatinine and lipid profile

Patients should have their feet examined at least annually for impaired sense of pressure, vibration, pain, or temperature, which is characteristic of peripheral neuropathy. Pressure sense is best tested with a monofilament esthesiometer (see Fig. 99-1). The entire foot, and especially skin beneath the metatarsal heads, should be examined for skin cracking and signs of ischemia, such as ulcerations, gangrene, fungal nail infections, deceased pulses, and hair loss.

Funduscopic examination should be done by an ophthalmologist; the screening interval is controversial but ranges from annually for patients with established retinopathy to every 3 yr for those without retinopathy on at least one examination.

Spot or 24-h urine testing is indicated annually to detect proteinuria or microalbuminuria, and serum creatinine should be measured to assess renal function.

Many physicians consider baseline electrocardiography important given the risk of heart disease. Lipid profile should be checked at least annually and more often when abnormalities are present. BP should be measured at every examination.

Treatment

• Diet and exercise

• For type 1 DM, insulin

• For type 2 DM, oral antihyperglycemics, insulin, or both

• Often ACE inhibitors, statins, and aspirin to prevent complications

Goals and methods: Treatment involves control of hyperglycemia to relieve symptoms and prevent complications while minimizing hypoglycemic episodes.

Goals for glycemic control are

• Blood glucose between 80 and 120 mg/dL (4.4 and 6.7 mmol/L) during the day

• Blood glucose between 100 and 140 mg/dL (5.6 and 7.8 mmol/L) at bedtime

• HbA_{1c} levels < 7%

Glucose levels are typically determined by home monitoring (see Monitoring: on p. 873). These goals may be adjusted for patients in whom strict glucose control may be inadvisable, such as the frail elderly; patients with a short life expectancy; patients who experience repeated bouts of hypoglycemia, especially with hypoglycemic unawareness; and patients who cannot communicate the presence of hypoglycemia symptoms (eg, young children).

Key elements for all patients are patient education, dietary and exercise counseling, and monitoring of glucose control.

All patients with type 1 DM require insulin.

Patients with type 2 DM and mildly elevated plasma glucose should be prescribed a trial of diet and exercise, followed by a single oral antihyperglycemic drug if lifestyle changes are insufficient, additional oral drugs as needed (combination therapy), and insulin when ≥ 2 drugs are ineffective for meeting recommended goals.

Patients with type 2 DM and more significant glucose elevations at diagnosis are typically prescribed lifestyle changes and oral antihyperglycemic drugs simultaneously.

Insulin is indicated as initial therapy for women with type 2 DM who are pregnant and for patients who present with acute metabolic decompensation, such as nonketotic hyperosmolar syndrome (NKHS) or DKA. Patients with severe hyperglycemia (plasma glucose > 400 mg/dL) may respond better to oral therapy after glucose levels are normalized with a brief period of insulin treatment.

Patients with impaired glucose regulation should receive counseling addressing their risk of developing DM and the importance of lifestyle changes for preventing DM. They should be monitored closely for development of DM symptoms or elevated plasma glucose. Ideal follow-up intervals have not been determined, but annual or biannual checks are probably appropriate.

Patient education: Education about causes of DM, diet, exercise, drugs, self-monitoring with fingerstick testing, and the symptoms and signs of hypoglycemia, hyperglycemia, and diabetic complications is crucial to optimizing care. Most patients with type 1 DM can also be taught how to adjust their insulin doses. Education should be reinforced at every physician visit and hospitalization. Formal diabetes education programs, generally conducted by diabetes nurses and nutrition specialists, are often very effective.

Diet: Adjusting diet to individual circumstances can help patients control fluctuations in their glucose level and, for patients with type 2 DM, lose weight.

In general, all patients with DM need to be educated about a diet that is low in saturated fat and cholesterol and contains moderate amounts of carbohydrate, preferably from whole grain sources with higher fiber content. Although dietary protein and fat contribute to caloric intake (and thus, weight gain or loss), only carbohydrates have a direct effect on blood glucose levels. A low-carbohydrate, high-fat diet improves glucose control for some patients, but its long-term safety is uncertain.

Patients with type 1 DM should use carbohydrate counting or the carbohydrate exchange system to match insulin dose to carbohydrate intake and facilitate physiologic insulin replacement. "Counting" the amount of carbohydrate in the meal is used to calculate the preprandial insulin dose. In general, patients require 1 unit of rapid-acting insulin for each 15 g of carbohydrate in a meal. This approach requires detailed patient education and is most successful when guided by a dietitian experienced in working with diabetic patients. Some experts advise use of the glycemic index to delineate between rapid and slowly metabolized carbohydrates, although others believe the index adds little.

Patients with type 2 DM should restrict calories, eat regularly, increase fiber intake, and limit intake of refined carbohydrates and saturated fats. Some experts also recommend dietary protein restriction to ≤ 0.8 g/kg/day to prevent progression of early nephropathy (see p. 2401). Nutrition consultation should complement physician counseling; the patient and the person who prepares the patient's meals should both be present.

Exercise: Physical activity should increase incrementally to whatever level a patient can tolerate. Some experts believe that aerobic exercise is better than isometric exercise for weight loss and protection from vascular disease, but resistance training also can improve glucose control, and all forms of exercise are beneficial.

Patients who experience hypoglycemic symptoms during exercise should be advised to test their blood glucose and ingest carbohydrates or lower their insulin dose as needed to get their glucose slightly above normal just before exercise. Hypoglycemia during vigorous exercise may require carbohydrate ingestion during the workout period, typically 5 to 15 g of sucrose or another simple sugar.

Patients with known or suspected cardiovascular disease may benefit from exercise stress testing before beginning an exercise program, while activity goals may need to be modified for patients with diabetic complications such as neuropathy and retinopathy.

Monitoring: DM control can be monitored by measuring blood levels of

• Glucose

• HbA_{1c}

• Fructosamine

Self-monitoring of whole blood glucose using fingertip blood, test strips, and a glucose meter is most important. It should be used to help patients adjust dietary intake and insulin and to help physicians recommend adjustments in the timing and doses of drugs.

Many different monitoring devices are available. Nearly all require test strips and a means for pricking the skin and obtaining a sample. Most come with control solutions, which should be used periodically to verify

proper meter calibration. Choice among devices is usually based on patient preferences for features such as time to results (usually 5 to 30 sec), size of display panel (large screens may benefit patients with poor eyesight), and need for calibration. Meters that allow for testing at sites less painful than fingertips (palm, forearm, upper arm, abdomen, thigh) are also available.

Continuous glucose monitoring systems using a subcutaneous catheter can provide real-time results, including an alarm to warn of hypoglycemia, hyperglycemia, or rapidly changing glucose levels. Such devices are expensive and do not eliminate the need for fingerstick glucose testing, but they may be useful for selected patients.

Patients with poor glucose control and those given a new drug or a new dose of a currently used drug may be asked to self-monitor 1 (usually morning fasting) to ≥ 5 times/day, depending on the patient's needs and abilities and the complexity of the treatment regimen. Most patients with type 1 DM benefit from testing at least 4 times/day.

HbA_{1c} levels reflect glucose control over the preceding 2 to 3 mo and hence assess control between physician visits. HbA_{1c} should be assessed quarterly in patients with type 1 DM and at least annually in patients with type 2 DM whose plasma glucose seems stable (more frequently when control is uncertain). Home testing kits are useful for patients who are able to follow the testing instructions rigorously.

Control suggested by HbA_{1C} values sometimes seems to differ from that suggested by daily glucose readings because of falsely elevated or normal values. False elevations may occur with renal insufficiency (urea interferes with the assay), low RBC turnover (as occurs with iron, folate, or vitamin B_{12} deficiency anemia), high-dose aspirin, and high blood alcohol concentrations. Falsely normal values occur with increased RBC turnover, as occurs with hemolytic anemias and hemoglobinopathies (eg, HbS, HbC) or during treatment of deficiency anemias.

Fructosamine, which is mostly glycosylated albumin but also comprises other glycosylated proteins, reflects glucose control in the previous 1 to 2 wk. Fructosamine monitoring may be used during intensive treatment of DM and for patients with Hb variants or high RBC turnover (which cause false HbA_{1c} results), but it is mainly used in research settings.

Urine glucose monitoring provides a crude indication of hyperglycemia and can be recommended only when blood glucose monitoring is impossible. By contrast, self-measurement of urine ketones is recommended for patients with type 1 DM if they experience symptoms, signs, or triggers of ketoacidosis, such as nausea or vomiting, abdominal pain, fever, cold or flu-like symptoms, or unusual sustained hyperglycemia (> 250 to 300 mg/dL) during glucose self-monitoring.

Insulin: Insulin is required for all patients with type 1 DM if they become ketoacidotic without it; it is also helpful for management of many patients with type 2 DM. Insulin replacement should ideally mimic β-cell function using 2 insulin types to provide basal and prandial requirements (physiologic replacement); this approach requires close attention to diet and exercise as well as to insulin timing and dose. Most insulin preparations are now recombinant human, practically eliminating the once-common allergic reactions to the drug when it was extracted from animal sources. Except for use of regular insulin IV in hospitalized patients, insulin is administered subcutaneously. A number of analogs, created by modifications of the human insulin molecule that alter subcutaneous absorption rates, are available.

Insulin types are commonly categorized by their time to onset and duration of action (see Table 99-3). However, these parameters vary within and among patients depending on many factors (eg, site and technique of injection,

[**Table 99-3.** Onset, Peak, and Duration of Action of Human Insulin Preparations*]

amount of subcutaneous fat, blood flow at the injection site).

Rapid-acting insulins, including lispro and aspart, are rapidly absorbed because reversal of an amino acid pair prevents the insulin molecule from associating into dimers and polymers. They begin to reduce

plasma glucose often within 15 min but have short duration of action (< 4 h). These insulins are best used at mealtime to control postprandial spikes in plasma glucose.

Regular insulin is slightly slower in onset (30 to 60 min) than lispro and aspart but lasts longer (6 to 8 h). It is the only form for IV use.

Neutral protamine Hagedorn (NPH, or insulin isophane) is intermediate-acting; onset of action is about 2 h after injection, peak effect is 4 to 12 h after injection, and duration of action is 18 to 26 h. Unlike NPH, insulin glargine has no discernible peak of action and provides a steady basal effect over 24 h. Combinations of NPH and regular insulin and of insulin lispro and lispro protamine (a form of lispro modified to act like NPH) are commercially available in premixed preparations (see Table 99-3).

Different insulin types can be drawn into the same syringe for injection but should not be premixed in bottles except by a manufacturer. On occasion, mixing insulins may affect rates of insulin absorption, producing variability of effect and making glycemic control less predictable, especially if mixed > 1 h before use. Insulin glargine should never be mixed with any other insulin.

Many prefilled insulin pen devices are available as an alternative to the conventional vial and syringe method. Insulin pens may be more convenient for use away from home and may be preferable for patients with limited vision or manual dexterity. Spring-loaded self-injection devices (for use with a syringe) may be useful for the occasional patient who is fearful of injection, and syringe magnifiers are available for patients with low vision.

Lispro, aspart, or regular insulin can also be given continuously using an insulin pump. Continuous subcutaneous insulin infusion pumps can eliminate the need for multiple daily injections, provide maximal flexibility in the timing of meals, and substantially reduce variability in glucose levels. Disadvantages include cost, mechanical failures leading to interruptions in insulin supply, and the inconvenience of wearing an external device. Frequent and meticulous self-monitoring and close attention to pump function are necessary for safe and effective use of the insulin pump.

Oligomeric or liposomal oral forms and transmucosal (eg, intranasal, oral spray) or transdermal delivery systems show promise but require further study.

Complications of insulin treatment: Hypoglycemia is the most common complication of insulin treatment, occurring more often as patients try to achieve strict glucose control and approach near-normoglycemia. Symptoms of mild or moderate hypoglycemia include headache, diaphoresis, palpitations, light-headedness, blurred vision, agitation, and confusion. Symptoms of more severe hypoglycemia include seizures and loss of consciousness. In older patients, hypoglycemia may cause strokelike symptoms of aphasia or hemiparesis and is more likely to precipitate stroke, MI, and sudden death. Patients with type 1 DM with long duration of disease may be unaware of hypoglycemic episodes because they no longer experience autonomic symptoms (hypoglycemia unawareness).

Patients should be taught to recognize symptoms of hypoglycemia, which usually respond rapidly to the ingestion of sugar, including candy, juice, and glucose tablets. Typically, 15 g of glucose or sucrose should be ingested. Patients should check their glucose levels 15 min after glucose or sucrose ingestion and ingest an additional 15 g if their glucose level is not > 80 mg/dL. For patients who are unconscious or unable to swallow, hypoglycemia can be treated immediately with glucagon 1 mg sc or IM or a 50% dextrose solution 50 mL IV (25 g) followed, if necessary, by IV infusion of a 5% or 10% dextrose solution to maintain adequate plasma glucose levels.

Hyperglycemia may follow hypoglycemia either because too much sugar was ingested or because hypoglycemia caused a surge in counter-regulatory hormones (glucagon, epinephrine, cortisol, growth hormone). Too high a bedtime insulin dose can drive glucose down and stimulate a counter-regulatory response, leading to morning hyperglycemia (Somogyi phenomenon). A more common cause of unexplained morning hyperglycemia, however, is a rise in early morning growth hormone (dawn phenomenon). In this case, the evening insulin dose should be increased, changed to a longer-acting preparation, or injected later.

Hypokalemia may be caused by intracellular shifts of K due to insulin-induced stimulation of the Na-K pump, but it is uncommon. Hypokalemia more commonly occurs in acute care settings where IV insulin is used.

Local allergic reactions at the site of insulin injections are rare, especially with the use of human insulins, but they may still occur in patients with latex allergy because of the natural rubber latex contained in vial stoppers. They can cause immediate pain or burning followed by erythema, pruritus, and induration the latter sometimes persist for days. Most reactions spontaneously disappear after weeks of continued injection and require no specific treatment, although antihistamines may provide symptomatic relief.

Generalized allergic reaction is extremely rare with human insulins but can occur when insulin is restarted after a lapse in treatment. Symptoms develop 30 min to 2 h after injection and include urticaria, angioedema, pruritus, bronchospasm, and anaphylaxis. Treatment with antihistamines often suffices, but epinephrine and IV glucocorticoids may be needed. If insulin treatment is needed after a generalized allergic reaction, skin testing with a panel of purified insulin preparations and desensitization should be done.

Local fat atrophy or hypertrophy at injection sites is relatively rare and is thought to result from an immune reaction to a component of the insulin preparation. Either may resolve by rotation of injection sites.

Insulin resistance occurs mostly in patients with type 2 DM. The causes are usually obesity and genetic factors. Circulating anti-insulin antibodies are a rare cause. This type of insulin resistance can sometimes be treated by changing insulin preparations (eg, from animal to human insulin) and by administering corticosteroids if necessary.

Insulin regimens for type 1 DM: Regimens range from twice/day split-mixed (eg, split doses of rapid- and intermediate-acting insulins) to more physiologic basal-bolus regimens using multiple daily injections (eg, single fixed [basal] dose of long-acting and variable prandial [bolus] doses of rapid-acting insulin) or an insulin pump. Intensive treatment, defined as glucose monitoring ≥ 4 times/day and ≥ 3 injections/day or continuous insulin infusion, is more effective than conventional treatment (1 to 2 insulin injections daily with or without monitoring) for preventing diabetic retinopathy, nephropathy, and neuropathy. However, intensive therapy may result in more frequent episodes of hypoglycemia and weight gain and is generally effective only in patients who are able and willing to take an active role in their self-care.

In general, most patients with type 1 DM can start with a total dose of 0.2 to 0.8 units of insulin/kg/day. Obese patients may require higher doses. Physiologic replacement involves giving 40 to 60% of the daily insulin dose as an intermediate- or long-acting preparation to cover basal needs, with the remainder given as a rapid- or short-acting preparation to cover postprandial increases. This approach is most effective when the dose of rapid- or short-acting insulin is determined by a sliding scale that takes into account preprandial blood glucose and anticipated meal content. Dose can be adjusted 1 to 2 units for each 50 mg/dL (2.7 mmol/L) above or below target glucose level. This physiologic regimen allows greater freedom of lifestyle because patients can skip or time-shift meals and maintain normoglycemia. However, no specific insulin regimen has proved more effective than others, and these recommendations are for initiation of therapy; thereafter, choice of regimens generally rests on physiologic response and patient and physician preferences.

Insulin regimens for type 2 DM: Regimens for type 2 DM also vary. In many patients, glucose levels are adequately controlled with lifestyle changes or oral drugs, but insulin should be added when glucose remains inadequately controlled by ≥ 2 oral drugs. Although uncommon, adult-onset type 1 DM may be the cause. Insulin should replace oral drugs in women who become pregnant. The rationale for combination therapy is strongest for use of insulin with oral biguanides and insulin sensitizers. Regimens vary from a single daily injection of long- or intermediate-acting insulin (usually at bedtime) to the multiple-injection regimen used by patients with type 1 DM. In general, the simplest effective regimen is preferred. Because of insulin resistance, some patients with type 2 DM require very large doses (> 2 units/kg/day). A common complication is weight gain, which is mostly attributable to reduction in loss of glucose in urine and improved metabolic efficiency.

Oral antihyperglycemic drugs: Oral anti-hyperglycemic drugs (see

Tables 99-4 and
99-5) are the primary treatment for type 2 DM, although insulin is often added when ≥ 2 oral drugs fail to provide adequate glycemic control. Oral antihyperglycemic drugs may

• Enhance pancreatic insulin secretion (secretagogues)

• Sensitize peripheral tissues to insulin (sensitizers)

• Impair GI absorption of glucose

Drugs with different mechanisms of action may be synergistic.

Sulfonylureas (SUs) are insulin secretagogues. They lower plasma glucose by stimulating pancreatic β-cell insulin secretion and may secondarily improve peripheral and hepatic insulin sensitivity by reducing glucose toxicity. First-generation drugs (see Table 99-4) are more likely to cause adverse effects and are used infrequently. All SUs promote hyperinsulinemia and weight gain of 2 to 5 kg, which over time may potentiate insulin resistance and limit their usefulness. All also can cause hypoglycemia. Risk factors include age > 65, use of long-acting drugs (especially chlorpropamide, glyburide, or glipizide), erratic eating and exercise, and renal or hepatic insufficiency. Hypoglycemia caused by long-acting drugs may last for days after treatment cessation, occasionally causes permanent neurologic disability, and can be fatal. For these reasons, some physicians hospitalize hypoglycemic patients, especially older ones. Chlorpropamide also causes the syndrome of inappropriate ADH secretion. Most patients taking SUs alone eventually require additional drugs to achieve normoglycemia, suggesting that SUs may exhaust β-cell function. However, worsening of insulin secretion and insulin resistance is probably more a feature of DM itself than of drugs used to treat it.

Short-acting insulin secretagogues (repaglinide, nateglinide) stimulate insulin secretion in a manner similar to SUs. They are faster acting, however, and may stimulate insulin secretion more during meals than at other times. Thus, they may be especially effective for reducing postprandial hyperglycemia and seem to have lower risk of hypoglycemia. There may be some weight gain, although apparently less than with SUs. Repaglinide seems to be as effective as SUs or metformin in lowering glucose levels. Nateglinide may be somewhat less effective and therefore more appropriate for patients with mild hyperglycemia. Patients who have not responded to other oral drug classes (eg, SUs, metformin) are not likely to respond to these drugs.

Biguanides lower plasma glucose by decreasing hepatic glucose production (gluconeogenesis and glycogenolysis). They are considered peripheral insulin sensitizers, but their stimulation of peripheral glucose uptake may simply be a result of reductions in glucose from their hepatic effects. Biguanides also lower lipid levels and may also decrease GI nutrient absorption, increase β-cell sensitivity to circulating glucose, and decrease levels of plasminogen activator inhibitor 1, thereby exerting an antithrombotic effect. Metformin is the only biguanide commercially available in the US. It is at least as effective as SUs in reducing plasma glucose, rarely causes hypoglycemia, and can be safely used with other drugs and insulin. In addition, metformin does not cause weight gain and may even promote weight loss by suppressing appetite. However, the drug commonly causes GI adverse effects (eg, dyspepsia, diarrhea), which for most people recede with time. Less commonly, metformin causes vitamin B_{12} malabsorption, but clinically

[**Table 99-4.** Characteristics of Oral Antihyperglycemics]

significant anemia is rare. Contribution of metformin to life-threatening lactic acidosis is controversial, but the drug is thought to be contraindicated in patients at risk of acidemia (including those with renal insufficiency [creatinine ≥ 1.4 mg/dL], heart failure, hypoxia or severe respiratory disease, alcoholism, other forms of metabolic acidosis, or dehydration). The drug should be withheld during surgery, administration of IV contrast, and any serious illness. Many people receiving metformin monotherapy eventually require an additional drug.

Thiazolidinediones (TZDs) decrease peripheral insulin resistance (insulin sensitizers), but their specific mechanisms of action are not well understood. The drugs bind a nuclear receptor primarily present in fat

cells (peroxisome-proliferator-activated receptor-γ [PPAR-γ]) that is involved in the transcription of genes that regulate glucose and lipid metabolism. TZDs also increase HDL levels, lower triglycerides, and may have anti-inflammatory and anti-atherosclerotic effects. TZDs are as effective as SUs and metformin in reducing HbA_{1C}. Because the drug class is relatively new, data on long-term safety and effectiveness are not available. Though one TZD (troglitazone) caused acute liver failure, currently available drugs have not proven hepatotoxic. Nevertheless, periodic monitoring of liver function is recommended. TZDs may cause peripheral edema, especially in patients taking insulin, and may worsen heart failure in susceptible patients. Weight gain, due to fluid retention and increased adipose tissue mass, is common and may be substantial (> 10 kg) in some patients. Rasiglitazone may increase risk of heart failure, angina, MI, stroke, and fracture.

α-Glucosidase inhibitors (AGIs) competitively inhibit intestinal enzymes that hydrolyze dietary carbohydrates; carbohydrates are digested and absorbed more slowly, thereby lowering postprandial plasma glucose. AGIs are less effective than other oral drugs in reducing plasma glucose, and patients often stop the drugs because they may cause dyspepsia, flatulence, and diarrhea. But the drugs are otherwise safe and can be used in combination with all other oral drugs and with insulin.

Dipeptidyl peptidase-4 inhibitors (eg, sitagliptin, saxagliptin) block glucagon-like peptide-1 (GLP-1) breakdown by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4). Vildagliptin, a similar drug, is being developed.

Injectable antihyperglycemic drugs: Injectable antihyperglycemic drugs other than insulin are the GLP-1 agonists and the amylin analog, pramlintide (see Table 99-4). These drugs are used in combination with other antihyperglycemics.

GLP-1 agonists (eg, exenatide [an incretin hormone], liraglutide) enhance glucose-dependent insulin secretion and slow gastric emptying. Exenatide may also reduce appetite and promote weight loss and stimulate β-cell proliferation. It is given by injection 5 or 10 µg bid before meals and may be used in combination with oral antihyperglycemics. Other GLP-1 agonists, including a long-acting form of exenatide, are being developed,.

The **amylin analog** pramlintide mimics amylin, a pancreatic β-cell hormone that helps regulate postprandial glucose levels. Pramlintide suppresses postprandial glucagon secretion, slows gastric emptying, and promotes satiety. It is given by injection and is used in combination with mealtime insulin. Patients with type 1 DM are given 30 to 60 µg sc before meals, and those with type 2 DM are given 120 µg.

Other antihyperglycemic treatments: Transplantation of pancreatic or islet cells is an alternative means of insulin delivery; both techniques effectively transplant insulin-producing

[**Table 99-5.** Combination Oral Antihyperglycemics]

β-cells into insulin-deficient (type 1) patients. Indications, tissue sources, procedures, and limitations of both procedures are discussed elsewhere (see p. 1138).

Other oral antihyperglycemic drugs are under investigation. These drugs include PPAR-α and PPAR-γ agonists (ragaglitazar, tesaglitazar); non-TZD insulin sensitizers, including recombinant human insulin-like growth factor-1 (IGF-1); and phosphodiesterase inhibitors, which augment pancreatic insulin secretion.

Adjunctive treatments: Measures to prevent or treat complications of DM are critical. ACE inhibitors, angiotensin II receptor blockers, or both are indicated for patients with evidence of early nephropathy (microalbuminuria or proteinuria), even in the absence of hypertension, and are a good choice for treating hypertension in patients who have DM and who have not yet shown renal impairment.

ACE inhibitors also help prevent cardiovascular events in patients with DM. Aspirin 81 to 325 mg once/day provides cardiovascular protection and should be used by most adults with DM in the absence of a specific contraindication. Patients with type 2 DM tend to have high levels of triglycerides and small, dense low-density lipoproteins (LDL) and low levels of HDL; they should receive aggressive treatment

with the same treatment goals as those of patients with known coronary artery disease (LDL < 100 mg/dL [< 2.6 mmol/L], HDL > 40 mg/dL [> 1.1 mmol/L], and triglycerides < 150 mg/dL [< 1.7 mmol/L]—see Table 100-4 on p. 897).

Orlistat, an intestinal lipase inhibitor, reduces dietary fat absorption; it reduces serum lipids and helps promote weight loss. Sibutramine, a centrally acting anorectic drug, is for short-term use to promote weight loss. Both of these drugs may be useful in selected patients as part of a comprehensive weight loss program. Surgical treatment for obesity, such as gastric banding or bypass, also leads to weight loss and improved glucose control in patients who have DM and are unable to lose weight through other means.

Regular professional podiatric care, including trimming of toenails and calluses, is important for patients with sensory loss or circulatory impairment. Such patients should be advised to inspect their feet daily for cracks, fissures, calluses, corns, and ulcers. Feet should be washed daily in lukewarm water, using mild soap, and dried gently and thoroughly. A lubricant (eg, lanolin) should be applied to dry, scaly skin. Nonmedicated foot powders should be applied to moist feet. Toenails should be cut, preferably by a podiatrist, straight across and not too close to the skin. Adhesive plasters and tape, harsh chemicals, corn cures, water bottles, and electric pads should not be used on skin. Patients should change stockings daily and not wear constricting clothing (eg, garters, socks or stockings with tight elastic tops). Shoes should fit well, be wide-toed without open heels or toes, and be changed frequently. Special shoes should be prescribed to reduce trauma if the foot is deformed (eg, previous toe amputation, hammer toe, bunion). Walking barefoot should be avoided. Patients with neuropathic foot ulcers should avoid weight bearing until ulcers heal. If they cannot, they should wear appropriate orthotic protection. Because most patients with these ulcers have little or no macrovascular occlusive disease, debridement and antibiotics frequently result in good healing and may prevent major surgery (see p. 672). After the ulcer has healed, appropriate inserts or special shoes should be prescribed. In refractory cases, especially if osteomyelitis is present, surgical removal of the metatarsal head (the source of pressure) or amputation of the involved toe or transmetatarsal amputation may be required. A neuropathic joint can often be satisfactorily managed with orthopedic devices (eg, short leg braces, molded shoes, sponge-rubber arch supports, crutches, prostheses).

All patients with DM should be vaccinated against *Streptococcus pneumoniae* (once) and influenza virus (annually).

Special Populations and Settings

The term brittle diabetes has been used to refer to patients who have dramatic, recurrent swings in glucose levels, often for no apparent reason. However, this concept has no biologic basis and should not be used. Labile plasma glucose levels are more likely to occur in patients with type 1 DM because endogenous insulin production is completely absent and, in some patients, counterregulatory response to hypoglycemia is impaired. Other causes include occult infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (eg, Addison's disease).

Patients with chronic difficulty maintaining acceptable glucose levels should be evaluated for situational factors that affect glucose control. Such factors include inadequate patient education or understanding that leads to errors in insulin administration, inappropriate food choices, and psychosocial stress that expresses itself in erratic patterns of drug use and food intake.

The initial approach is to thoroughly review self-care techniques, including insulin preparation and injection and glucose testing. Increased frequency of self-testing may reveal previously unrecognized patterns and provides the patient with helpful feedback. A thorough dietary history, including timing of meals, should be taken to identify potential contributions to poor control. Underlying disorders should be ruled out by physical examination and appropriate laboratory tests. For some insulin-treated patients, changing to a more intensive regimen that allows for frequent dose adjustments (based on glucose testing) is helpful. In some cases, the frequency of hypoglycemic and hyperglycemic episodes diminishes over time even without specific treatment, suggesting life circumstances may contribute to causation.

Children: Children with type 1 DM require physiologic insulin replacement as do adults, and similar

treatment regimens, including insulin pumps, are used. However, the risk of hypoglycemia, because of unpredictable meal and activity patterns and limited ability to report hypoglycemic symptoms, may require modification of treatment goals. Most young children can be taught to actively participate in their own care, including glucose testing and insulin injections. School personnel and other caregivers must be informed about the disease and instructed about the detection and treatment of hypoglycemic episodes. Screening for microvascular complications can generally be deferred until after puberty.

Children with type 2 DM require the same attention to diet and weight control and recognition and management of dyslipidemia and hypertension as do adults. Most children with type 2 DM have severe obesity, so lifestyle modification is the cornerstone of therapy. Children with mild hyperglycemia generally begin treatment with metformin unless they have ketosis, renal insufficiency, or another contraindication to metformin use. Dosage is 500 to 1000 mg bid. If response is insufficient, an insulin secretagogue (such as a SU or repaglinide) or insulin may be added. TZDs are generally avoided because long-term safety is unknown.

Adolescents: Glucose control typically deteriorates as children with DM enter adolescence. Multiple factors contribute, including pubertal and insulin-induced weight gain; hormonal changes that decrease insulin sensitivity; psychosocial factors that lead to insulin nonadherence (eg, mood and anxiety disorders); family conflict, rebellion, and peer pressure; eating disorders that lead to insulin omission as a means of controlling weight; and experimentation with cigarettes, alcohol, and substance use. For these reasons, some adolescents experience recurrent episodes of hyperglycemia and DKA requiring emergency department visits and hospitalization.

Treatment often involves intensive medical supervision combined with psychosocial interventions (eg, mentoring or support groups), individual or family therapy, and psychopharmacology when indicated. Patient education is important so that adolescents can safely enjoy the freedoms of early adulthood. Rather than judging personal choices and behaviors, providers must continually reinforce the need for careful glycemic control, especially frequent blood sugar monitoring and use of frequent, low-dose, fast-acting insulins as needed.

Hospitalization: Diabetes can be a primary reason for hospitalization or can accompany other illnesses that require inpatient care. All diabetic patients with DKA, NKHS, or prolonged or severe hypoglycemia should be hospitalized. Others with SU-induced hypoglycemia, poorly controlled hyperglycemia, or acute worsening of diabetic complications may benefit from brief hospitalization, as do children and adolescents with new-onset disease. Control may worsen on discharge when insulin regimens developed in controlled inpatient settings prove inadequate to the uncontrolled conditions outside the hospital.

When other illnesses mandate hospitalization, many patients do well without any change in drugs. However, glucose control may prove difficult, and it is often neglected when other diseases are more acute. Restricted physical activity and acute illness worsen hyperglycemia in some patients, whereas dietary restrictions and symptoms that accompany illness (eg, nausea, vomiting, diarrhea, anorexia) precipitate hypoglycemia in others—especially when antihyperglycemic drug doses remain unchanged. In addition, it may be difficult to control glucose adequately in hospitalized patients because usual routines (eg, timing of meals, drugs, and procedures) are inflexibly timed relative to diabetes treatment regimens. Inpatients who are able to eat may continue usual outpatient regimens; others may be appropriately treated with basal insulin without or with supplemental short-acting insulin. Slidingscale insulin should not be the only intervention to correct hyperglycemia; it is reactive rather than proactive, and no data suggest it leads to outcomes equivalent to or better than other approaches. Longer-acting insulins should be adjusted to prevent hyperglycemia rather than just using short-acting insulins to correct it.

Inpatient hyperglycemia worsens short-term prognosis for many acute conditions, most notably stroke and acute MI, and often prolongs hospital stay. Critical illness causes insulin resistance and hyperglycemia even in patients without known DM. Insulin infusion to maintain plasma glucose between 100 and 150 mg/dL (4.4 and 6.1 mmol/L) prevents adverse outcomes such as organ failure, may enhance recovery from stroke, and leads to improved survival in patients requiring prolonged (> 5 days) critical care. Severely ill patients, especially those receiving glucocorticoids or pressors, may need very high doses of insulin (> 5 to 10 units/h) because of insulin resistance. Insulin infusion should also be considered for patients receiving TPN and for patients with type 1 DM who cannot ingest anything orally.

Surgery: The physiologic stress of surgery can increase plasma glucose in patients with DM and induce DKA in those with type 1 DM. For type 1 patients, one half to two thirds of the usual morning dose of intermediate-acting insulin or 70 to 80% of the dose of long-acting insulin (glargine or detemir) can be given the morning before surgery with an IV infusion of a 5% dextrose solution at a rate of 100 to 150 mL/h. During and after surgery, plasma glucose (and ketones if hyperglycemia suggests the need) should be measured at least every 2 h. Glucose infusion is continued (monitoring is done at 2- to 4-h intervals), and regular or short-acting insulin is given sc q 4 to 6 h as needed to maintain the plasma glucose level between 100 and 200 mg/dL (5.55 and 11.01 mmol/L) until the patient can be switched to oral feedings and resume the usual insulin regimen. Additional doses of intermediate- or long-acting insulin should be given if there is a substantial delay (> 24 h) in resuming the usual regimen. This approach may also be used for insulin-treated patients with type 2 DM, but frequent measurement of ketones may be omitted.

Some physicians prefer to withhold sc insulin on the day of surgery and to give insulin by IV infusion. One approach is to add 6 to 10 units of regular insulin to 1 L of 5% dextrose in 0.9% saline solution or water infused initially at 100 to 150 mL/h on the morning of surgery based on the plasma glucose level. Alternatively, separate insulin (1 to 2 units/h) and dextrose (75 to 125 mL/h of 5% dextrose) infusions may be used and allow for easier titration. Insulin adsorption onto IV tubing can lead to inconsistent effects, which can be minimized by preflushing the IV tubing with insulin solution. Insulin infusion is continued through recovery, with insulin adjusted based on the plasma glucose levels obtained in the recovery room and at 1- to 2-h intervals thereafter.

Most patients with type 2 DM who are treated with oral antihyperglycemic drugs maintain acceptable glucose levels when fasting and may not require insulin in the perioperative period. Most oral drugs, including SUs and metformin, should be withheld on the day of surgery, and plasma glucose levels should be measured preoperatively and postoperatively and every 6 h while patients receive IV fluids. Oral drugs may be resumed when patients are able to eat, but metformin should be withheld until normal renal function is confirmed 48 h after surgery.

Prevention

Type 1: No treatments definitely prevent the onset or progression of type 1 DM. Azathioprine, corticosteroids, and cyclosporine induce remission of early type 1 DM in some patients, presumably through suppression of autoimmune β-cell destruction. However, toxicity and the need for lifelong treatment limit their use. In a few patients, short-term treatment with anti-CD3 monoclonal antibodies reduces insulin requirements for at least the first year of recent-onset disease by suppressing autoimmune T-cell response.

Type 2: Type 2 DM usually can be prevented with lifestyle modification. Weight loss of as little as 7% of baseline body weight, combined with moderate-intensity physical activity (eg, walking 30 min/day), may reduce the incidence of DM in high-risk people by > 50%. Metformin and acarbose have also been shown to reduce the risk of DM in patients with impaired glucose regulation. TZDs may also be protective, perhaps by inducing PPAR-γ activity but require further study before they can be recommended for routine preventive use.

Complications: Risk of DM complications can be decreased by strict control of plasma glucose, defined as HbA_{1c} < 7%, and by control of hypertension and lipid levels (see pp. 2069 and 896). Specific measures for prevention of progression of complications once detected are described under Complications (see p. 868) and Treatment (see p. 871).

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is an acute metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. DKA occurs mostly in type 1 diabetes mellitus (DM). It causes nausea, vomiting, and abdominal pain and can progress to cerebral edema, coma, and death. DKA is diagnosed by detection of hyperketonemia and anion gap metabolic acidosis in the presence of hyperglycemia. Treatment involves volume expansion, insulin replacement, and prevention of hypokalemia.

DKA is most common among patients with type 1 DM and develops when insulin levels are insufficient to meet the body's basic metabolic requirements. DKA is the first manifestation of type 1 DM in a minority of patients. Insulin deficiency can be absolute (eg, during lapses in the administration of exogenous insulin) or relative (eg, when usual insulin doses do not meet metabolic needs during physiologic stress). Common physiologic stresses that can trigger DKA include acute infection (particularly pneumonia and UTI), MI, stroke, pancreatitis, and trauma. Drugs implicated in causing DKA include corticosteroids, thiazide diuretics, and sympathomimetics. DKA is less common in type 2 DM, but it may occur in situations of unusual physiologic stress.

Pathophysiology

Insulin deficiency causes the body to metabolize triglycerides and muscle instead of glucose for energy. Serum levels of glycerol and free fatty acids (FFAs) rise because of unrestrained lipolysis, as does alanine because of muscle catabolism. Glycerol and alanine provide substrate for hepatic gluconeogenesis, which is stimulated by the excess of glucagon that accompanies insulin deficiency. Glucagon also stimulates mitochondrial conversion of FFAs into ketones. Insulin normally blocks ketogenesis by inhibiting the transport of FFA derivatives into the mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. The major ketoacids produced, acetoacetic acid and β-hydroxybutyric acid, are strong organic acids that create metabolic acidosis. Acetone derived from the metabolism of acetoacetic acid accumulates in serum and is slowly disposed of by respiration.

Hyperglycemia due to insulin deficiency causes an osmotic diuresis that leads to marked urinary losses of water and electrolytes. Urinary excretion of ketones obligates additional losses of Na and K. Serum Na may fall from natriuresis or rise due to excretion of large volumes of free water. K is also lost in large quantities, sometimes > 300 mEq/24 h. Despite a significant total body deficit of K, initial serum K is typically normal or elevated because of the extracellular migration of K in response to acidosis. K levels generally fall further during treatment as insulin therapy drives K into cells. If serum K is not monitored and replaced as needed, life-threatening hypokalemia may develop.

Symptoms and Signs

Symptoms and signs of DKA include those of hyperglycemia (see p. 868) with the addition of nausea, vomiting, and—particularly in children—abdominal pain. Lethargy and somnolence are symptoms of more severe decompensation. Patients may be hypotensive and tachycardic from dehydration and acidosis; they may breathe rapidly and deeply to compensate for acidemia (Kussmaul's respirations). They may also have fruity breath due to exhaled acetone. Fever is not a sign of DKA itself and, if present, signifies underlying infection. In the absence of timely treatment, DKA progresses to coma and death.

Acute cerebral edema, a complication in about 1% of DKA patients, occurs primarily in children and less often in adolescents and young adults. Headache and fluctuating level of consciousness herald this complication in some patients, but respiratory arrest is the initial manifestation in others. The cause is not well understood but may be related to too-rapid reductions in serum osmolality or to brain ischemia. It is most likely to occur in children < 5 yr when DKA is the initial manifestation of DM. Children with the highest BUN and lowest $PaCO_2$ at presentation seem to be at greatest risk. Delays in correction of hyponatremia and the use of HCO_3 during DKA treatment are additional risk factors.

Diagnosis

• Arterial pH

• Serum ketones

• Calculation of anion gap

In patients suspected of having DKA, serum electrolytes, BUN and creatinine, glucose, ketones, and osmolarity should be measured. Urine should be tested for ketones. Patients who appear significantly ill and those with positive ketones should have ABG measurement. DKA is diagnosed by an arterial pH <

7.30 with an anion gap > 12 (see Sidebar 98-1 on p. 858) and serum ketones in the presence of hyperglycemia. A presumptive diagnosis can be made when urine glucose and ketones are strongly positive. Urine test strips and some assays for serum ketones may underestimate the degree of ketosis because they detect acetoacetic and not β-hydroxybutyric acid, which is usually the predominant ketoacid.

Symptoms and signs of a triggering illness should be pursued with appropriate studies (eg, cultures, imaging studies). Adults should have an ECG to screen for acute MI and to help determine the significance of abnormalities in serum K.

Other laboratory abnormalities include hyponatremia, elevated serum creatinine, and elevated serum osmolarity. Hyperglycemia may cause dilutional hyponatremia, so measured serum Na is corrected by adding 1.6 mEq/L for each 100 mg/dL elevation of serum glucose over 100 mg/dL. To illustrate, for a patient with serum Na of 124 mEq/L and glucose of 600 mg/dL, add 1.6 ([600-100]/100) = 8 mEq/L to 124 for a corrected serum Na of 132 mEq/L. As acidosis is corrected, serum K drops. An initial K level < 4.5 mEq/L indicates marked K depletion and requires immediate K supplementation. Serum amylase and lipase are often elevated, even in the absence of pancreatitis (which may be present in alcoholic DKA patients and in those with coexisting hypertriglyceridemia).

Prognosis

Mortality rates for DKA are between 1 and 10%. Shock or coma on admission indicates a worse prognosis. Main causes of death are circulatory collapse, hypokalemia, and infection. Among children with cerebral edema, 57% recover completely, 21% survive with neurologic sequelae, and 21% die.

Treatment

• IV 0.9% saline

• Correction of any hypokalemia

• IV insulin (as long as serum K is ≥ 3.3 mEq/L)

• Rarely IV $NaHCO_3$ (if pH < 7 after 1 h of treatment)

The most urgent goals are rapid intravascular volume repletion, correction of hyperglycemia and acidosis, and prevention of hypokalemia. Identification of precipitating factors is also important. Treatment should occur in intensive care settings because clinical and laboratory assessments are initially needed every hour or every other hour with appropriate adjustments in treatment.

Intravascular volume should be restored rapidly to raise BP and ensure glomerular perfusion; once intravascular volume is restored, remaining total body water deficits are corrected more slowly, typically over about 24 h. Initial volume repletion in adults is typically achieved with rapid IV infusion of 1 to 3 L of 0.9% saline solution, followed by saline infusions at 1 L/h or faster as needed to raise BP, correct hyperglycemia, and keep urine flow adequate. Adults with DKA typically need a minimum of 3 L of saline over the first 5 h. When BP is stable and urine flow adequate, normal saline is replaced by 0.45% saline. When plasma glucose falls to < 250 mg/dL, IV fluid should be changed to 5% dextrose in 0.45% saline.

For children, fluid deficits are estimated at 60 to 100 mL/kg body weight. Maintenance fluids (for ongoing losses) must also be provided (see p. 2808). Initial fluid therapy should be 0.9% saline (20 mL/kg) over 1 to 2 h, followed by 0.45% saline once BP is stable and urine output adequate. The remaining fluid deficit should be replaced over 36 h, typically requiring a rate (including maintenance fluids) of about 2 to 4 mL/kg/h, depending on the degree of dehydration.

Hyperglycemia is corrected by giving regular insulin 0.15 unit/kg IV bolus initially, followed by continuous IV infusion of 0.1 unit/kg/h in 0.9% saline solution. *Insulin should be withheld until serum K is ≥ 3.3 mEq/L* (see p. 886). Insulin adsorption onto IV tubing can lead to inconsistent effects, which can be minimized by preflushing the IV tubing with insulin solution. If plasma glucose does not fall by 50 to 75

mg/dL in the first hour, insulin doses should be doubled. Children should be given a continuous IV insulin infusion of 0.1 unit/kg/h or higher with or without a bolus.

Ketones should begin to clear within hours if insulin is given in sufficient doses. However, clearance of ketones may seem to lag because of conversion of β-hydroxybutyrate to acetoacetate (which is the "ketone" measured in most hospital laboratories) as acidosis resolves. Serum pH and HCO_3 levels should also quickly improve, but restoration of a normal serum HCO_3 level may take 24 h. Rapid correction of pH by HCO_3 administration may be considered if pH remains < 7 after about an hour of initial fluid resuscitation, but HCO_3 is associated with development of acute cerebral edema (primarily in children) and should not be used routinely. If used, only modest pH elevation should be attempted (target pH of about 7.1), with doses of 50 to 100 mEq over 30 to 60 min, followed by repeat measurement of arterial pH and serum K.

When plasma glucose becomes 250 to 300 mg/dL (13.88 to 16.65 mmol/L) in adults, 5% dextrose should be added to IV fluids to reduce the risk of hypoglycemia. Insulin dosage can then be reduced (minimum 1 to 2 units/h), but the continuous IV infusion of regular insulin should be maintained until the anion gap has narrowed and blood and urine are consistently negative for ketones. Insulin replacement may then be switched to regular insulin 5 to 10 units sc q 4 to 6 h. When the patient is stable and able to eat, a typical split-mixed or basal-bolus insulin regimen is begun. IV insulin should be continued for 1 to 4 h after the initial dose of sc insulin is given. Children should continue to receive 0.05 unit/kg/h insulin infusion until sc insulin is initiated and pH is > 7.3.

Hypokalemia prevention requires replacement of 20 to 30 mEq K in each liter of IV fluid to keep serum K between 4 and 5 mEq/L. If serum K is < 3.3 mEq/L, insulin should be withheld and K given at 40 mEq/h until serum K is ≥ 3.3 mEq/L; if serum K is > 5 mEq/L, K supplementation can be withheld. Initially normal or elevated serum K measurements may reflect shifts from intracellular stores in response to acidemia and belie the true K deficits that almost all DKA patients have. Insulin replacement rapidly shifts K into cells, so levels should be checked hourly or every other hour in the initial stages of treatment. Hypophosphatemia often develops during treatment of DKA, but phosphate repletion is of unclear benefit in most cases. If indicated (eg, if rhabdomyolysis, hemolysis, or neurologic deterioration occurs), K phosphate 1 to 2 mmol/kg of phosphate, can be infused over 6 to 12 h. If K phosphate is given, the serum Ca level usually decreases and should be monitored.

Treatment of suspected cerebral edema is hyperventilation, corticosteroids, and mannitol, but these measures are often ineffective after the onset of respiratory arrest.

Nonketotic Hyperosmolar Syndrome

(Hyperosmolar Hyperglycemic State)

Nonketotic hyperosmolar syndrome (NKHS) is a metabolic complication of diabetes mellitus (DM) characterized by hyperglycemia, extreme dehydration, hyperosmolar plasma, and altered consciousness. It most often occurs in type 2 DM, often in the setting of physiologic stress. NKHS is diagnosed by severe hyperglycemia and serum hyperosmolarity and absence of significant ketosis. Treatment is IV saline solution and insulin. Complications include coma, seizures, and death.

NKHS is a complication of type 2 DM and has a mortality rate of up to 40%. It usually develops after a period of symptomatic hyperglycemia in which fluid intake is inadequate to prevent extreme dehydration due to hyperglycemia-induced osmotic diuresis. The precipitating factor may be a coexisting acute infection, drugs that impair glucose tolerance (glucocorticoids) or increase fluid loss (diuretics), medical nonadherence, or other medical conditions. Serum ketones are not present because the amounts of insulin present in most patients with type 2 DM are adequate to suppress ketogenesis. Because symptoms of acidosis are not present, most patients endure a significantly longer period of osmotic dehydration before presentation, and thus plasma glucose (> 600 mg/dL [> 33 mmol/L]) and osmolarity (> 320 mOsm/L) are typically much higher than in diabetic ketoacidosis (DKA).

Symptoms and Signs

The primary symptom of NKHS is altered consciousness varying from confusion or disorientation to coma, usually as a result of extreme dehydration with or without prerenal azotemia, hyperglycemia, and hyperosmolarity. In contrast to DKA, focal or generalized seizures and transient hemiplegia may occur.

Diagnosis

• Blood glucose level

• Serum osmolarity

Generally, NKHS is initially suspected when a markedly elevated glucose level is found in a fingerstick specimen obtained in the course of a workup of altered mental status. If measurements have not already been obtained, measurement of serum electrolytes, BUN and creatinine, glucose, ketones, and osmolarity should be done. Urine should be tested for ketones. Serum K levels are usually normal, but Na may be low or high depending on volume deficits. BUN and serum creatinine levels are markedly increased. Arterial pH is usually > 7.3, but occasionally mild metabolic acidosis develops due to lactate accumulation.

The average fluid deficit is 10 L, and acute circulatory collapse is a common cause of death. Widespread thrombosis is a frequent finding on autopsy, and in some cases bleeding may occur as a consequence of disseminated intravascular coagulation. Other complications include aspiration pneumonia, acute renal failure, and acute respiratory distress syndrome.

Treatment

• IV 0.9% saline

• Correction of any hypokalemia

• IV insulin (as long as serum K is ≥ 3.3 mEq/L)

Treatment is 0.9% saline solution 1 L IV over 30 min, then at 1 L/h to raise BP and improve circulation and urine output. It can be replaced by 0.45% saline when BP becomes normal and plasma glucose reaches 300 mg/dL. The rate of infusion of IV fluids should be adjusted depending on BP, cardiac status, and the balance between fluid input and output.

Insulin is given at 0.15 unit/kg IV bolus followed by a 0.1 unit/kg/h infusion after the first liter of saline has been infused. Hydration alone can sometimes precipitously decrease plasma glucose, so insulin dose may need to be reduced. A too-quick reduction in osmolality can lead to cerebral edema. Occasional patients with insulin-resistant type 2 DM with NKHS require larger insulin doses. Once plasma glucose reaches 200 to 250 mg/dL, insulin infusion should be reduced to basal levels (1 to 2 units/h) until rehydration is complete and the patient is able to eat. Addition of 5% dextrose infusion may occasionally be needed to avoid hypoglycemia. After recovery from the acute episode, patients are usually switched to adjusted doses of sc insulin. Most patients can resume using oral antihyperglycemic drugs once their condition is stable.

K replacement is similar to DKA: 40 mEq/h for serum K < 3.3 mEq/L; 20 to 30 mEq/h for serum K between 3.3 and 4.9 mEq/L; and none for serum K ≥ 5 mEq/L.

Alcoholic Ketoacidosis

Alcoholic ketoacidosis is a metabolic complication of alcohol use and starvation characterized by hyperketonemia and anion gap metabolic acidosis without significant hyperglycemia. Alcoholic ketoacidosis causes nausea, vomiting, and abdominal pain. Diagnosis is by history and findings of ketoacidosis without hyperglycemia. Treatment is IV saline solution and dextrose infusion.

Alcoholic ketoacidosis is attributed to the combined effects of alcohol and starvation on glucose metabolism.

Pathophysiology

Alcohol diminishes hepatic gluconeogenesis and leads to decreased insulin secretion, increased lipolysis, impaired fatty acid oxidation, and subsequent ketogenesis. Counter-regulatory hormones are increased and may further inhibit insulin secretion. Plasma glucose levels are usually low or normal, but mild hyperglycemia sometimes occurs.

Symptoms and Signs

Typically, an alcohol binge leads to vomiting and the cessation of alcohol or food intake for ≥ 24 h. During this period of starvation, vomiting continues and abdominal pain develops, leading the patient to seek medical attention. Pancreatitis may occur.

Diagnosis

• Clinical evaluation

• Calculation of anion gap

• Exclusion of other disorders

Diagnosis requires a high index of suspicion; similar symptoms in an alcoholic patient may result from acute pancreatitis, methanol or ethylene glycol poisoning, or diabetic ketoacidosis (DKA). In patients suspected of having alcoholic ketoacidosis serum electrolytes (including Mg), BUN and creatinine, glucose, ketones, amylase, lipase, and osmolarity should be measured. Urine should be tested for ketones. Patients who appear significantly ill and those with positive ketones should probably have ABG and serum lactate measurement. The absence of hyperglycemia makes DKA improbable. Those with mild hyperglycemia may have underlying diabetes mellitus, which may be recognized by elevated levels of glycosylated Hb (HbA_{1C}). Typical laboratory findings include a high anion gap metabolic acidosis, ketonemia, and low levels of K, Mg, and P. Detection of acidosis may be complicated by concurrent metabolic alkalosis due to vomiting, resulting in a relatively normal pH; the main clue is the elevated anion gap. If history does not rule out toxic alcohol ingestion as a cause of the elevated anion gap, serum methanol and ethylene glycol levels should be obtained. Ca oxalate crystals in the urine also suggests ethylene glycol poisoning. Lactic acid levels are often elevated because of hypoperfusion and the altered balance of reduction and oxidation reactions in the liver.

Treatment

• IV thiamin and other vitamins plus Mg

• IV 5% dextrose in 0.9% saline

Treatment begins with an IV infusion of 5% dextrose in 0.9% saline solution, preceded by thiamin 100 mg IV to prevent development of Wernicke's encephalopathy or Korsakoff's psychosis. Initial IV fluids should contain added water-soluble vitamins and Mg, with K replacement as required. Ketoacidosis and GI symptoms usually respond rapidly. Use of insulin is appropriate only if there is any question of atypical DKA or if hyperglycemia > 300 mg/dL develops.

Hypoglycemia

Hypoglycemia unrelated to exogenous insulin therapy is an uncommon clinical syndrome characterized by low plasma glucose level, symptomatic sympathetic nervous system stimulation, and CNS dysfunction. Many drugs and disorders cause it. Diagnosis requires blood tests done at the time of symptoms or during a 72-h fast. Treatment is provision of glucose

combined with treatment of the underlying disorder.

Most commonly, symptomatic hypoglycemia is a complication of drug treatment of diabetes mellitus (DM). Oral antihyperglycemics or insulin may be involved.

Symptomatic hypoglycemia unrelated to treatment of DM is relatively rare, in part because the body has extensive counter-regulatory mechanisms to compensate for low blood glucose levels. Glucagon and epinephrine levels surge in response to acute hypoglycemia and seem to be the first line of defense. Cortisol and growth hormone levels also increase acutely and are important in the recovery from prolonged hypoglycemia. The threshold for release of these hormones is usually above that for hypoglycemic symptoms.

Etiology

Causes of physiologic hypoglycemia can be classified as

• Reactive (postprandial) or fasting

• Insulin-mediated or non-insulin-mediated

• Drug-induced or nondrug-induced

Insulin-mediated causes include exogenous administration of insulin or an insulin secretagogue and insulin-secreting tumors (insulinomas). A helpful practical classification is based on clinical status: whether hypoglycemia occurs in patients who appear healthy or ill. Within these categories, causes of hypoglycemia can be divided into drug-induced and other causes. Pseudohypoglycemia occurs when processing of blood specimens in untreated test tubes is delayed and cells, such as RBCs and leukocytes (especially if increased, as in leukemia or polycythemia), consume glucose. Factitious hypoglycemia is true hypoglycemia induced by nontherapeutic administration of sulfonylureas or insulin.

Symptoms and Signs

The surge in autonomic activity in response to low plasma glucose causes sweating, nausea, warmth, anxiety, tremulousness, palpitations, and possibly hunger and paresthesias. Insufficient glucose supply to the brain causes headache, blurred or double vision, confusion, difficulty speaking, seizures, and coma. In controlled settings, autonomic symptoms begin at or beneath a plasma glucose level of about 60 mg/dL (3.33 mmol/L), whereas CNS symptoms occur at or below a glucose level of about 50 mg/dL (2.78 mmol/L). However, symptoms suggestive of hypoglycemia are far more common than the condition itself. Most people with glucose levels at these thresholds have no symptoms, and most people with symptoms suggestive of hypoglycemia have normal glucose concentrations.

Diagnosis

• Blood glucose level correlated with clinical findings

• Response to dextrose (or other sugar) administration

• Sometimes 72-h fast

• Sometimes insulin, C-peptide, and proinsulin levels

In principle, diagnosis requires verification that a low plasma glucose level (< 50 mg/dL [< 2.78 mmol/L]) exists at the time hypoglycemic symptoms occur and that the symptoms are responsive to dextrose administration. If a practitioner is present when symptoms occur, blood should be sent for glucose testing. If glucose is normal, hypoglycemia is ruled out and no further testing is needed. If glucose is abnormally low, serum insulin, C-peptide, and proinsulin measured from the same tube can distinguish insulin-mediated from non-insulin-mediated and factitious from physiologic hypoglycemia and can obviate the need for further testing. Insulin growth factor 2 (IGF-2) levels may help identify non-islet cell (IGF-2

secreting) tumors, which are an unusual cause of hypoglycemia.

In practice, however, it is unusual that practitioners are present when patients experience symptoms suggestive of hypoglycemia. Home glucose meters are unreliable for quantifying hypoglycemia, and there are no clear glycosylated Hb (HbA_{1C}) thresholds that distinguish long-term hypoglycemia from normoglycemia. So the need for more extensive diagnostic testing is based on the probability that an underlying disorder that could cause hypoglycemia exists given a patient's clinical appearance and coexisting illnesses.

A 72-h fast done in a controlled setting is the standard for diagnosis. Patients drink only noncaloric, noncaffeinated beverages, and plasma glucose is measured at baseline, whenever symptoms occur, and q 4 to 6 h or q 1 to 2 h if glucose falls below 60 mg/dL (3.3 mmol/L). Serum insulin, C-peptide, and proinsulin should be measured at times of hypoglycemia to distinguish endogenous from exogenous (factitious) hypoglycemia. The fast is terminated at 72 h if the patient has experienced no symptoms and glucose remains normal, sooner if glucose decreases to ≤ 45 mg/dL (≤ 2.5 mmol/L) in the presence of hypoglycemic symptoms. End-of-fast measurements include β-hydroxybutyrate (which should be low in insulinoma), serum sulfonylurea to detect drug-induced hypoglycemia, and plasma glucose after IV glucagon injection to detect an increase characteristic of insulinoma. Sensitivity, specificity, and predictive values for detecting hypoglycemia by this protocol have not been reported. There is no definitive lower limit of glucose that unequivocally defines pathologic hypoglycemia during a 72-h fast. Normal women tend to have lower fasting glucose levels than men and may have glucose levels as low as 30 mg/dL without symptoms. If symptomatic hypoglycemia has not occurred by 72 h, the patient should exercise vigorously for about 30 min. If hypoglycemia still does not occur, insulinoma is essentially excluded and further testing is generally not indicated.

Treatment

• Oral sugar or IV dextrose

• Sometimes parenteral glucagon

Immediate treatment of hypoglycemia involves provision of glucose. Patients able to eat or drink can drink juices, sucrose water, or glucose solutions; eat candy or other foods; or chew on glucose tablets when symptoms occur. Infants and younger children may be given 10% dextrose solution 2 to 5 mL/kg IV bolus. Adults and older children unable to eat or drink can be given glucagon 0.5 (< 20 kg) or 1 mg (≥ 20 kg) sc or IM or 50% dextrose 50 to 100 mL IV bolus, with or without a continuous infusion of 5 to 10% dextrose solution sufficient to resolve symptoms. The efficacy of glucagon depends on the size of hepatic glycogen stores; glucagon has little effect on plasma glucose in patients who have been fasting or who are hypoglycemic for long periods.

Underlying disorders causing hypoglycemia must also be treated. Islet cell and non-islet cell tumors must first be localized, then removed by enucleation or partial pancreatectomy; about 6% recur within 10 yr. Diazoxide and octreotide can be used to control symptoms while the patient is awaiting surgery or when a patient refuses or is not a candidate for a procedure. Islet cell hypertrophy is most often a diagnosis of exclusion after an islet cell tumor is sought but not identified. Drugs that cause hypoglycemia, including alcohol, must be stopped. Treatment of hereditary and endocrine disorders; hepatic, renal, and heart failure; and sepsis and shock are described elsewhere.

Chapter 100. Lipid Disorders

Introduction

Lipids are fats that are either absorbed from food or synthesized by the liver. Triglycerides (TGs) and cholesterol contribute most to disease, although all lipids are physiologically important. The primary function of TGs is to store energy in adipocytes and muscle cells; cholesterol is a ubiquitous constituent of cell membranes, steroids, bile acids, and signaling molecules. All lipids are hydrophobic and mostly insoluble in blood, so they require transport within hydrophilic, spherical structures called lipoproteins, which possess surface proteins (apoproteins, or apolipoproteins) that are cofactors and ligands for lipid-processing enzymes (see Table 100-1). Lipoproteins are classified by size and density (defined as the ratio of lipid to protein) and are important because high levels of low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL) are major risk factors for atherosclerotic heart disease (see p. 2081).

Physiology

Pathway defects in lipoprotein synthesis, processing, and clearance can lead to accumulation of atherogenic lipids in plasma and endothelium.

Exogenous (dietary) lipid metabolism: Over 95% of dietary lipids are TGs; the rest are phospholipids, free fatty acids (FFAs), cholesterol (present in foods as esterified cholesterol), and fat-soluble vitamins. Dietary TGs are digested in the stomach and duodenum into monoglycerides (MGs) and FFAs by gastric lipase, emulsification from vigorous stomach peristalsis, and pancreatic lipase. Dietary cholesterol esters are de-esterified into free cholesterol by these same mechanisms. MGs, FFAs, and free cholesterol are then solubilized in the intestine by bile acid micelles, which shuttle them to intestinal villi for absorption. Once absorbed into the enterocyte, they are reassembled into TGs and packaged with cholesterol into chylomicrons, the largest lipoproteins.

[**Table 100-1.** Major Apoproteins and Enzymes Important to Lipid Metabolism]

Chylomicrons transport dietary TGs and cholesterol from within enterocytes through lymphatics into the circulation. In the capillaries of adipose and muscle tissue, apoprotein C-II (apo C-II) on the chylomicron activates endothelial lipoprotein lipase (LPL) to convert 90% of chylomicron TG to fatty acids and glycerol, which are taken up by adipocytes and muscle cells for energy use or storage. Cholesterol-rich chylomicron remnants then circulate back to the liver, where they are cleared in a process mediated by apoprotein E (apo E).

Endogenous lipid metabolism: Lipoproteins synthesized by the liver transport endogenous TGs and cholesterol. Lipoproteins circulate through the blood continuously until the TGs they contain are taken up by peripheral tissues or the lipoproteins themselves are cleared by the liver. Factors that stimulate hepatic lipoprotein synthesis generally lead to elevated plasma cholesterol and TG levels.

Very-low-density lipoproteins (VLDL) contain apoprotein B-100 (apo B), are synthesized in the liver, and transport TGs and cholesterol to peripheral tissues. VLDL is the way the liver exports excess TGs derived from plasma FFA and chylomicron remnants; VLDL synthesis increases with increases in intrahepatic FFA, such as occur with high-fat diets and when excess adipose tissue releases FFAs directly into the circulation (eg, in obesity, uncontrolled diabetes mellitus). Apo C-II on the VLDL surface activates endothelial LPL to break down TGs into FFAs and glycerol, which are taken up by cells.

Intermediate-density lipoproteins (IDL) are the product of LPL processing of VLDL and chylomicrons. IDL are cholesterol-rich VLDL and chylomicron remnants that are either cleared by the liver or metabolized by hepatic lipase into LDL, which retains apo B.

Low-density lipoproteins (LDL), the products of VLDL and IDL metabolism, are the most cholesterol-rich of all lipoproteins. About 40 to 60% of all LDL are cleared by the liver in a process mediated by apo B and hepatic LDL receptors. The rest are taken up by either hepatic LDL or nonhepatic non-LDL (scavenger) receptors. Hepatic LDL receptors are down-regulated by delivery of cholesterol to the liver

by chylomicrons and by increased dietary saturated fat; they can be up-regulated by decreased dietary fat and cholesterol. Nonhepatic scavenger receptors, most notably on macrophages, take up excess oxidized circulating LDL not processed by hepatic receptors. Monocytes rich in oxidized LDL migrate into the subendothelial space and become macrophages; these macrophages then take up more oxidized LDL and form foam cells within atherosclerotic plaques (see p. 2081). There are 2 forms of LDL: large, buoyant and small, dense LDL. Small, dense LDL is especially rich in cholesterol esters, associated with metabolic disturbances such as hypertriglyceridemia and insulin resistance, and especially atherogenic. The increased atherogenicity of small, dense LDL derives from less efficient hepatic LDL receptor binding, leading to prolonged circulation and exposure to endothelium and increased oxidation.

High-density lipoproteins (HDL) are initially cholesterol-free lipoproteins that are synthesized in both enterocytes and the liver. HDL metabolism is complex, but HDL's overall role is to obtain cholesterol from peripheral tissues and other lipoproteins and transport it to where it is needed most—other cells, other lipoproteins (using cholesteryl ester transfer protein [CETP]), and the liver (for clearance). Its overall effect is anti-atherogenic. Efflux of free cholesterol from cells is mediated by ATP-binding cassette transporter A1 (ABCA1), which combines with apoprotein A-I (apo A-I) to produce nascent HDL. Free cholesterol in nascent HDL is then esterified by the enzyme lecithin-cholesterol acyl transferase (LCAT), producing mature HDL. Blood HDL levels may not completely represent reverse cholesterol transport.

Lipoprotein (a) [Lp (a)] is LDL that contains apoprotein(a), characterized by 5 cysteine-rich regions called kringles. One of these regions is homologous with plasminogen and is thought to competitively inhibit fibrinolysis and thus predispose to thrombus. The Lp(a) may also directly promote atherosclerosis. The metabolic pathways of Lp(a) production and clearance are not well characterized, but levels increase in patients with diabetic nephropathy.

Dyslipidemia

(Hyperlipidemia)

Dyslipidemia is *elevation* of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins. Treatment is dietary changes, exercise, and lipid-lowering drugs.

There is no natural cutoff between normal and abnormal lipid levels because lipid measurements are continuous. A linear relation probably exists between lipid levels and cardiovascular risk, so many people with "normal" cholesterol levels benefit from achieving still lower levels. Consequently, there are no numeric definitions of dyslipidemia; the term is applied to lipid levels for which treatment has proved beneficial. Proof of benefit is strongest for lowering elevated low-density lipoprotein (LDL) levels. In the overall population, evidence is less strong for a benefit from lowering elevated TG and increasing low high-density lipoprotein (HDL) levels, in part because elevated TG and low HDL levels are more predictive of cardiovascular risk in women than in men.

HDL levels do not always predict cardiovascular risk. For example, high HDL levels caused by some genetic disorders may not protect against cardiovascular disorders, and low HDL levels caused by some genetic disorders may not increase the risk of cardiovascular disorders. Although HDL levels predict cardiovascular risk in the overall population, the increased risk may be caused by other factors, such as accompanying lipid and metabolic abnormalities, rather than the HDL level itself.

Classification

Dyslipidemias were traditionally classified by patterns of elevation in lipids and lipoproteins (Fredrickson phenotype—see Table 100-2). A more practical system categorizes dyslipidemias as primary or secondary and characterizes them by increases in cholesterol only (pure or isolated hypercholesterolemia), increases in TGs only (pure or isolated hypertriglyceridemia), or increases in both cholesterol and TGs (mixed or combined hyperlipidemias). This system does not take into account specific lipoprotein abnormalities (eg,

low HDL or high LDL) that may contribute to disease despite normal cholesterol and TG levels.

Etiology

Primary (genetic) causes and secondary (lifestyle and other) causes contribute to dyslipidemias in varying degrees. For example, in familial combined hyperlipidemia, expression may occur only in the presence of significant secondary causes.

Primary causes: Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol, or in underproduction or excessive clearance of HDL (see Table 100-3). Primary disorders, the most common cause of dyslipidemia in children, do not cause a large percentage of cases in adults. The names of many reflect an old nomenclature in which lipoproteins were detected and distinguished by how they separated into α (HDL) and β (LDL) bands on electrophoretic gels.

[**Table 100-2.** Lipoprotein Patterns (Fredrickson Phenotypes)]

Secondary causes: Secondary causes contribute to most cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats. Trans fats are polyunsaturated or monounsaturated fatty acids to which hydrogen atoms have been added; they are commonly used in many processed foods and are as atherogenic as saturated fat. Other common secondary causes include diabetes mellitus, alcohol overuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis and other cholestatic liver diseases, and drugs, such as thiazides, β-blockers, retinoids, highly active antiretroviral agents, estrogen and progestins, and glucocorticoids.

Diabetes is an especially significant secondary cause because patients tend to have an atherogenic combination of high TGs; high small, dense LDL fractions; and low HDL (diabetic dyslipidemia, hypertriglyceridemic hyperapo B). Patients with type 2 diabetes are especially at risk. The combination may be a consequence of obesity, poor control of diabetes, or both, which may increase circulating free fatty acids (FFAs), leading to increased hepatic very-low-density lipoprotien (VLDL) production. TG-rich VLDL then transfers TG and cholesterol to LDL and HDL, promoting formation of TG-rich, small, dense LDL and clearance of TG-rich HDL. Diabetic dyslipidemia is often exacerbated by the increased caloric intake and physical inactivity that characterize the lifestyles of some patients with type 2 diabetes. Women with diabetes may be at special risk of cardiac disease from this form.

[**Table 100-3.** Genetic (Primary) Dyslipidemias]

Symptoms and Signs

Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD) and peripheral arterial disease. High levels of TGs (> 1000 mg/dL [> 11.3 mmol/L]) can cause acute pancreatitis. High levels of LDL can cause eyelid xanthelasmas; arcus corneae; and tendinous xanthomas at the Achilles, elbow, and knee tendons and over metacarpophalangeal joints. Patients with the homozygous form of familial hypercholesterolemia may have the above findings plus planar or cutaneous xanthomas. Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet. Patients with the rare dysbetalipoproteinemia can have palmar and tuberous xanthomas.

Severe hypertriglyceridemia (> 2000 mg/dL [> 22.6 mmol/L]) can give retinal arteries and veins a creamy white appearance (lipemia retinalis). Extremely high lipid levels also give a lactescent (milky) appearance to blood plasma. Symptoms can include paresthesias, dypsnea, and confusion.

Diagnosis

- Serum lipid profile (measured total cholesterol, TG, and HDL cholesterol and calculated LDL cholesterol and VLDL)

Dyslipidemia is suspected in patients with characteristic physical findings or complications of dyslipidemia (eg, atherosclerotic disease). Primary lipid disorders are suspected when patients have physical signs of dyslipidemia, onset of premature atherosclerotic disease (at < 60 yr), a family history of atherosclerotic disease, or serum cholesterol > 240 mg/dL (> 6.2 mmol/L). Dyslipidemia is diagnosed by measuring serum lipids. Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL cholesterol, and LDL cholesterol.

Lipid profile measurement: TC, TGs, and HDL cholesterol are measured directly; TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL. TC values vary by 10% and TGs by up to 25% day-to-day even in the absence of a disorder. TC and HDL cholesterol can be measured in the non-fasting state, but most patients should have all lipids measured while fasting for maximum accuracy and consistency.

Testing should be postponed until after resolution of acute illness, because TGs increase and cholesterol levels decrease in inflammatory states. Lipid profiles can vary for about 30 days after an acute MI; however, results obtained within 24 h after MI are usually reliable enough to guide initial lipid-lowering therapy.

LDL cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol concentration in VLDL particles is usually one fifth of the total lipid in the particle. Thus, LDL cholesterol = TC - [HDL cholesterol + (TGs ÷ 5)] (Friedewald formula). This calculation is valid only when TGs are < 400 mg/dL and patients are fasting, because eating increases TGs. The calculated LDL cholesterol value incorporates measures of all non-HDL, nonchylomicron cholesterol, including that in IDL and lipoprotein (a) [Lp(a)]. LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients with elevated TGs, but these direct measurements are not routinely necessary. The role of apoprotein B testing is under study because values reflect all non-HDL cholesterol (in VLDL, VLDL remnants, IDL, and LDL) and may be more predictive of CAD risk than LDL alone.

Other tests: Patients with premature atherosclerotic cardiovascular disease, cardiovascular disease with normal or near-normal lipid levels, or high LDL levels refractory to drug therapy should probably have Lp(a) levels measured. Lp(a) levels may also be directly measured in patients with borderline high LDL cholesterol levels to determine whether drug therapy is warranted. C-reactive protein and homocysteine measurement may be considered in the same populations.

Secondary causes: Tests for secondary causes of dyslipidemia—including measurements of fasting glucose, liver enzymes, creatinine, thyroid-stimulating hormone (TSH), and urinary protein—should be done in most patients with newly diagnosed dyslipidemia and when a component of the lipid profile has inexplicably changed for the worse.

Screening: A fasting lipid profile (TC, TGs, HDL cholesterol, and calculated LDL cholesterol) should be obtained in all adults ≥ 20 yr and should be repeated every 5 yr. Lipid measurement should be accompanied by assessment of other cardiovascular risk factors, defined as

- Diabetes mellitus
- Cigarette use
- Hypertension
- Family history of CAD in a male 1st-degree relative before age 55 or a female 1st-degree relative before age 65

A definite age after which patients no longer require screening has not been established, but evidence supports screening of patients into their 80s, especially in the presence of atherosclerotic cardiovascular disease.

Indications for screening patients < 20 yr are atherosclerotic risk factors, such as diabetes, hypertension, cigarette smoking, and obesity; premature CAD in a parent, grandparent, or sibling; or a cholesterol level > 240 mg/dL (> 6.2 mmol/L) or known dyslipidemia in a parent. If information on relatives is unavailable, as in the case of adopted children, screening is at the discretion of the health care practitioner.

Patients with an extensive family history of heart disease should also be screened by measuring Lp(a) levels.

Treatment

• Risk assessment by explicit criteria

• Lifestyle changes (eg, exercise, dietary modification)

• For high LDL cholesterol, statins, sometimes bile acid sequestrants, ezetimibe, and other measures

• For high TG or low HDL cholesterol, niacin, fibrates, and sometimes other measures

General principles: Treatment is indicated for all patients with cardiovascular disease (secondary prevention) and for some without (primary prevention). The National Institutes of Health's National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines are the most common reference for deciding which adults should be treated (see Tables 100-4 and 100-5). The guidelines focus primarily on reducing elevated LDL cholesterol levels and secondarily on treating high TGs, low HDL, and metabolic syndrome (see p. 64). An alternate treatment guide (the Sheffield table) uses TC:HDL ratios combined with presence of CAD risk factors to predict cardiovascular risk, but this approach probably leads to undertreatment.

Treatment of children is controversial; dietary changes may be difficult to implement, and no data suggest that lowering lipid levels in childhood effectively prevents heart disease in adulthood. Moreover, the safety and effectiveness of long-term lipid-lowering treatment are questionable. Nevertheless, the American Academy of Pediatrics (AAP) recommends treatment for some children who have elevated LDL cholesterol levels.

Treatment options depend on the specific lipid abnormality, although different lipid abnormalities often coexist. In some patients, a single abnormality may require several therapies; in others, a single treatment may be adequate for several abnormalities. Treatment should always include treatment of hypertension and diabetes, smoking cessation, and in patients

[**Table 100-4.** National Cholesterol Education Program Adult Treatment Panel III Approach to Dyslipidemias]

with a 10-yr risk of MI or death from CAD of ≥ 10% (as determined from the Framingham tables—see Tables 100-6 and 100-7), low-dose daily aspirin. In general, treatment options for men and women are the same.

Elevated LDL cholesterol: In **adults**, ATPIII guidelines recommend treatment for those with any of the following:

• Elevated LDL cholesterol levels and a history of CAD

• Conditions that confer a risk of future cardiac events similar to that of CAD itself (CAD equivalents, defined as diabetes mellitus, abdominal aortic aneurysm, peripheral arterial disease, and symptomatic carotid artery disease)

• ≥ 2 CAD risk factors

ATPIII guidelines recommend that these patients have LDL cholesterol levels lowered to < 100 mg/dL, but accumulating evidence

[**Table 100-5.** Ncep Adult Treatment Panel III Guidelines for Treatment of Hyperlipidemia]

suggests that this target may be too high and a target LDL cholesterol < 70 mg/dL is an option for patients at very high risk (eg, patients with known CAD and diabetes, other poorly controlled risk factors, metabolic syndrome, or acute coronary syndrome). When drugs are used, a dose providing at least a 30 to 40% decrease in LDL cholesterol is desirable (see Table 100-8).

For **children**, the AAP recommends dietary treatment for children with LDL cholesterol > 110 mg/dL. Drug therapy is recommended for children > 8 yr and with either of the following:

- Poor response to dietary therapy, LDL cholesterol ≥ 190 mg/dL, and no family history of premature cardiovascular disease
- LDL cholesterol ≥ 160 mg/dL and a family history of premature cardiovascular disease or ≥ 2 risk factors for premature cardiovascular disease

Childhood risk factors besides family history and diabetes include cigarette smoking, hypertension, low HDL cholesterol (< 35 mg/dL), obesity, and physical inactivity.

Treatment options to lower LDL cholesterol in all age groups include lifestyle changes (diet and exercise), drugs, dietary supplements, procedural interventions, and experimental therapies. Many of these options are also effective for treating other lipid abnormalities. Exercise lowers LDL cholesterol in some people; it is also essential to maintain ideal body weight. Dietary changes and exercise should be the initial approach whenever feasible.

Lifestyle changes can involve diet and exercise. Dietary changes include decreasing intake of saturated fats and cholesterol; increasing the proportion of dietary fiber, and complex carbohydrates; and maintaining ideal body weight. Referral to a dietitian is often useful, especially for older people. The length

[**Table 100-6.** Framingham Risk Tables for Men]

of time for which lifestyle changes should be attempted before beginning lipid-lowering drugs is controversial. In patients at average or low cardiovascular risk, 3 to 6 mo is reasonable. Generally, 2 to 3 visits with a patient over 2 to 3 mo are sufficient to assess motivation and adherence.

Drugs are the next step when lifestyle changes are not effective. However, for patients with extremely elevated LDL cholesterol (> 200 mg/dL [> 5.2 mmol/L]) and those at high cardiovascular risk, drug therapy should accompany diet and exercise from the start.

Statins are the drugs and possibly treatment of choice for LDL cholesterol reduction; they demonstrably reduce cardiovascular mortality. Statins inhibit hydroxymethylglutaryl CoA reductase, a key enzyme in cholesterol synthesis, leading to up-regulation of LDL receptors and increased LDL clearance. They reduce LDL cholesterol by up to 60% and produce small increases in HDL and modest decreases in TGs. Statins also seem to decrease intraarterial inflammation, systemic inflammation, or both by stimulating production of endothelial nitric oxide and may have other beneficial effects. Adverse effects are uncommon but include liver enzyme elevations and myositis or rhabdomyolysis. Muscle toxicity without enzyme elevation has also been reported. Adverse effects are more common among older patients, patients with several disorders, and patients taking several drugs. In some patients, changing from one statin to another or lowering the dose relieves the problem. Muscle toxicity seems to be most common when some of the statins are used with drugs that inhibit cytochrome P3A4 (eg, macrolide antibiotics, azole antifungals, cyclosporine) and with fibrates, especially gemfibrozil. Properties of statins differ

[**Table 100-7.** Framingham Risk Tables for Women]

slightly by drug, and the choice of drug should be based on patient characteristics, LDL cholesterol level, and provider discretion (see Table 100-8).

Bile acid sequestrants block intestinal bile acid reabsorption, forcing up-regulation of hepatic LDL receptors to recruit circulating cholesterol for bile synthesis. They are proved to reduce cardiovascular mortality. Bile acid sequestrants are usually used with statins or with nicotinic acid (see p. 903) to augment LDL cholesterol reduction and are the drugs of choice for children and women who are or are planning to become pregnant. Bile acid sequestrants are safe, but their use is limited by adverse effects of bloating, nausea, cramping, and constipation. They may also increase TGs, so their use is contraindicated in patients with hypertriglyceridemia. Cholestyramine and colestipol, but not colesevelam, interfere with absorption of other drugs—notably thiazides, β-blockers, warfarin, digoxin, and thyroxine—an effect that can be decreased by administration 4 h before or 1 h after other drugs.

Cholesterol absorption inhibitors, such as ezetimibe, inhibit intestinal absorption of cholesterol and phytosterol. Ezetimibe usually lowers LDL cholesterol by 15 to 20% and causes small increases in HDL and a mild decrease in TGs. Ezetimibe can be used as monotherapy in patients intolerant to statins or added to statins for patients on maximum doses with persistent LDL cholesterol elevation. Adverse effects are infrequent.

Dietary supplements that lower LDL cholesterol levels include fiber supplements and commercially available margarines and other products containing plant sterols (sitosterol and campesterol) or stanols. The latter reduce LDL cholesterol by up to 10% without affecting HDL or TGs by competitively displacing cholesterol from intestinal micelles.

[**Table 100-8.** Lipid-Lowering Drugs]

Procedural approaches are reserved for patients with severe hyperlipidemia (LDL cholesterol > 300 mg/dL) that is refractory to conventional therapy, such as occurs with familial hypercholesterolemia. Options include LDL apheresis (in which LDL is removed by extracorporeal plasma exchange), ileal bypass (to block reabsorption of bile acids), liver transplantation (which transplants LDL receptors), and portocaval shunting (which decreases LDL production by unknown mechanisms). LDL apheresis is the procedure of choice in most instances when maximally tolerated therapy fails to lower LDL adequately. Apheresis is also the usual therapy in patients with the homozygous form of familial hypercholesterolemia who have limited or no response to drug therapy.

Future therapies to reduce LDL include peroxisome proliferator-activated receptor agonists that have thiazolidinedione-like and fibrate-like properties, LDL-receptor activators, LPL activators, and recombinant apo E. Cholesterol vaccination (to induce anti-LDL antibodies and hasten LDL clearance from serum) and gene transfer are conceptually appealing therapies that are under study but years away from being available for use.

Elevated TGs: Though it is unclear whether elevated TGs independently contribute to cardiovascular disease, they are associated with multiple metabolic abnormalities that contribute to CAD (eg, diabetes, metabolic syndrome). Consensus is emerging that lowering elevated TGs is beneficial (see Table 100-4). No target goals exist, but levels < 150 mg/dL (< 1.7 mmol/L) are generally considered desirable. No guidelines specifically address treatment of elevated TGs in children.

The **overall treatment strategy** is to first implement lifestyle changes, including exercise, weight loss, and avoidance of concentrated dietary sugar and alcohol. Intake of 2 to 4 servings/wk of marine fish high in ω-3 fatty acids may be effective, but the amount of ω-3 fatty acids is often lower than needed; supplements may be helpful. In patients with diabetes, glucose levels should be tightly controlled. If these measures are ineffective, lipid-lowering drugs should be considered. Patients with very high TGs should begin drug therapy at diagnosis to more quickly reduce the risk of acute pancreatitis.

Fibrates reduce TGs by about 50%. They seem to stimulate endothelial LPL, leading to increased fatty acid oxidation in the liver and muscle and decreased hepatic VLDL synthesis. They also increase HDL by up to 20%. Fibrates can cause GI adverse effects, including dyspepsia, abdominal pain, and elevated

liver enzymes. They uncommonly cause cholelithiasis. Fibrates may potentiate muscle toxicity when used with statins and potentiate the effects of warfarin.

Nicotinic acid may also be useful (see below).

Statins can be used in patients with TGs < 500 mg/dL if LDL cholesterol elevations are also present; statins may reduce both LDL cholesterol and TGs through reduction of VLDL. If only TGs are elevated, fibrates are the drug of choice.

Omega-3 fatty acids in high doses (1 to 6 g/day of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) can be effective in reducing TGs. The ω-3 fatty acids EPA and DHA are the active ingredients in marine fish oil or ω-3 capsules. Adverse effects include eructation and diarrhea. These may be decreased by giving the fish oil capsules with meals in divided doses (eg, bid or tid). Omega-3 fatty acids can be a useful adjunct to other therapies.

Low HDL: Treatment to increase HDL cholesterol levels may decrease risk of death, but data are limited. ATPIII guidelines define low HDL cholesterol as < 40 mg/dL [< 1.04 mmol/L]; the guidelines do not specify an HDL cholesterol target level and recommend interventions to raise HDL cholesterol only after LDL cholesterol targets have been reached. Treatments for LDL cholesterol and TG reduction often increase HDL cholesterol, and the 3 objectives can sometimes be achieved simultaneously. No guidelines specifically address treatment of low HDL cholesterol in children.

Treatment includes **lifestyle changes** such as an increase in exercise and weight loss. Alcohol raises HDL cholesterol but is not routinely recommended as a therapy because of its many other adverse effects. Drugs are useful when lifestyle changes alone are insufficient.

Nicotinic acid (niacin) is the most effective drug for increasing HDL. Its mechanism of action is unknown, but it seems to both increase HDL production and inhibit HDL clearance; it may also mobilize cholesterol from macrophages. Niacin also decreases TGs and, in doses of 1500 to 2000 mg/day, reduces LDL cholesterol. Niacin causes flushing, pruritus, and nausea; premedication with low-dose aspirin may prevent these adverse effects. Extended-release preparations cause flushing less often. However, most OTC slow-release preparations are not recommended; an exception is polygel controlled-release niacin. Niacin can cause liver enzyme elevations and occasionally liver failure, insulin resistance, and hyperuricemia and gout. It may also increase homocysteine levels. In patients with average LDL cholesterol and below-average HDL cholesterol levels, niacin combined with statin treatment may be effective in preventing cardiovascular disorders.

Fibrates increase HDL. Infusion of recombinant HDL (eg, apoprotein A-1 Milano, an HDL variant in which a cysteine is substituted for an arginine at position 173 allowing for dimer formation) seems promising as a treatment for atherosclerosis but requires further study.

Elevated Lp(a): The upper limit of normal for Lp(a) is about 30 mg/dL (0.8 mmol/L), but values in African Americans run higher. Few data exist to guide the treatment of elevated Lp(a) or to establish treatment efficacy. Niacin is the only drug that directly decreases Lp(a); it can lower Lp(a) by ≤ 20% at higher doses. The usual approach in patients with elevated Lp(a) is to lower LDL cholesterol aggressively.

Secondary causes: Treatment of diabetic dyslipidemia should always involve lifestyle changes, with statins to reduce LDL cholesterol, fibrates to decrease TGs, or both drugs. Metformin lowers TGs, which may be a reason to choose it over other oral antihyperglycemic drugs when treating diabetes. Some thiazolidinediones (TZDs) increase both HDL cholesterol and LDL cholesterol (probably the less atherogenic large, buoyant type of LDL). Some TZDs also decrease TGs. These antihyperglycemic drugs should not be chosen over lipid-lowering drugs to treat lipid abnormalities in diabetic patients but may be useful adjuncts. Patients with very high TG levels and less than optimally controlled diabetes may have better response to insulin than to oral antihyperglycemic drugs.

Treatment of dyslipidemia in patients with hypothyroidism, renal disease, liver disease, or a combination of these disorders involves treating the underlying disorders primarily and lipid abnormalities secondarily. Abnormal lipid levels in patients with low-normal thyroid function (high-normal TSH levels) improve with

hormone replacement. Reducing the dosage of or stopping drugs that cause lipid abnormalities should be considered.

Monitoring treatment: Lipid levels should be monitored periodically after starting treatment. No data support specific monitoring intervals, but measuring lipid levels 2 to 3 mo after starting or changing therapies and once or twice yearly after lipid levels are stabilized is common practice.

Despite the low incidence of liver and muscle toxicity with statin use (0.5 to 2% of all users), current recommendations are for baseline measurements of liver and muscle enzyme levels at the beginning of treatment. Many practitioners obtain at least one additional set of liver enzyme measurements 4 to 12 wk after beginning treatment and annually thereafter. Statin therapy can be continued unless liver enzymes increase to > 3 times the upper limit of normal. Muscle enzyme levels need not be checked regularly unless patients develop myalgias or other muscle symptoms. If statin-induced muscle damage is suspected, statin use is stopped and CK may be measured. When muscle symptoms subside, a lower dose or a different statin can be tried.

Elevated High-Density Lipoprotein Levels

Elevated high-density lipoprotein (HDL) level is HDL cholesterol > 80 mg/dL (> 2.1 mmol/L).

Elevated HDL cholesterol levels usually correlate with decreased cardiovascular risk; however, high HDL cholesterol levels caused by some genetic disorders may not protect against cardiovascular disease, probably because of accompanying lipid and metabolic abnormalities.

Primary causes are single or multiple genetic mutations that result in overproduction or decreased clearance of HDL. Secondary causes of high HDL cholesterol include all of the following:

• Chronic alcoholism without cirrhosis

• Primary biliary cirrhosis

• Hyperthyroidism

• Drugs (eg, corticosteroids, insulin, phenytoin)

The unexpected finding of high HDL cholesterol in patients not taking lipid-lowering drugs should prompt a diagnostic evaluation for a secondary cause with measurements of AST, ALT, and thyroid-stimulating hormone; a negative evaluation suggests a possible primary cause.

Cholesteryl ester transfer protein (CETP) deficiency is a rare autosomal recessive disorder caused by a *CETP* gene mutation. CETP facilitates transfer of cholesterol esters from HDL to other lipoproteins, and CETP deficiency affects low-density lipoprotein (LDL) cholesterol and slows HDL clearance. Affected patients display no symptoms or signs but have HDL cholesterol > 150 mg/dL. Protection from cardiovascular disorders has not been proved. No treatment is necessary.

Familial hyperalphalipoproteinemia is an autosomal dominant condition caused by various unidentified and known genetic mutations, including those that cause apoprotein A-I overproduction and apoprotein C-III variants. The disorder is usually diagnosed incidentally when plasma HDL cholesterol levels are > 80 mg/dL. Affected patients have no other symptoms or signs. No treatment is necessary.

Hypolipidemia

Hypolipidemia is a decrease in plasma lipoprotein caused by primary (genetic) or secondary factors. It is usually asymptomatic and diagnosed incidentally on routine lipid screening. Treatment of secondary hypolipidemia involves treating underlying disorders. Treatment of primary hypolipidemia is often unnecessary, but patients with some genetic disorders require high-dose vitamin E and dietary supplementation of fats and other fat-soluble vitamins.

Etiology

Hypolipidemia is defined as a total cholesterol (TC) < 120 mg/dL (< 3.1 mmol/L) or low-density lipoprotein (LDL) cholesterol < 50 mg/dL (< 0.13 mmol/L). Secondary causes are far more common than primary causes and include all of the following:

• Hyperthyroidism

• Chronic infections and other inflammatory states

• Hematologic and other cancers

• Undernutrition (including that accompanying chronic alcohol use)

• Malabsorption

The unexpected finding of low cholesterol or low LDL cholesterol in a patient not taking a lipid-lowering drug should prompt a diagnostic evaluation, including measurements of AST, ALT, and thyroid-stimulating hormone; a negative evaluation suggests a possible primary cause.

There are 3 primary disorders in which single or multiple genetic mutations result in underproduction or increased clearance of LDL.

Abetalipoproteinemia (Bassen-Kornzweig syndrome): This autosomal recessive condition is caused by mutations in the gene for microsomal triglyceride (TG) transfer protein, a protein critical to chylomicron and very-low-density lipoprotein (VLDL) formation. Dietary fat cannot be absorbed, and lipoproteins in both metabolic pathways are virtually absent from serum; TC is typically < 45 mg/dL (< 1.16 mmol/L), TGs are < 20 mg/dL (< 0.23 mmol/L), and LDL is undetectable. The condition is often first noticed in infants with fat malabsorption, steatorrhea, and failure to thrive. Intellectual disability may result. Because vitamin E is distributed to peripheral tissues via VLDL and LDL, most affected people eventually develop severe vitamin E deficiency. Symptoms and signs include visual changes from slow retinal degeneration, sensory neuropathy, posterior column signs, and cerebellar signs of dysmetria, ataxia, and spasticity, which can eventually lead to death. RBC acanthocytosis is a distinguishing feature on blood smear. Diagnosis is made by the absence of apoprotein B (apo B) in plasma; intestinal biopsies show lack of microsomal transfer protein. Treatment is with high doses (100 to 300 mg/kg once/day) of vitamin E with supplementation of dietary fat and other fat-soluble vitamins. The prognosis is poor.

Hypobetalipoproteinemia: Hypobetalipoproteinemia is an autosomal dominant or codominant condition caused by mutations in the gene coding for apo B. Heterozygous patients have truncated apo B, leading to rapid LDL clearance. Heterozygous patients manifest no symptoms or signs except for TC < 120 mg/dL and LDL cholesterol < 80 mg/dL. TGs are normal. Homozygous patients have either shorter truncations, leading to lower lipid levels (TC < 80 mg/dL, LDL cholesterol < 20 mg/dL), or absent apo B synthesis, leading to symptoms and signs of abetalipoproteinemia. Diagnosis is by finding low levels of LDL cholesterol and apo B; hypobetalipoproteinemia and abetalipoproteinemia are distinguished from one another by family history. People who are heterozygous and people who are homozygous with low but detectable LDL cholesterol require no treatment. Treatment of people who are homozygous with no LDL is the same as for abetalipoproteinemia.

Chylomicron retention disease: Chylomicron retention disease is a very rare autosomal recessive condition caused by an unknown mutation leading to deficient apo B secretion from enterocytes. Chylomicron synthesis is absent, but VLDL synthesis remains intact. Affected infants have fat malabsorption, steatorrhea, and failure to thrive and may develop neurologic disorders similar to those in abetalipoproteinemia. Diagnosis is by intestinal biopsy of patients with low cholesterol levels and absence of postprandial chylomicrons. Treatment is supplementation of fat and fatsoluble vitamins.

Chapter 101. Amyloidosis

Amyloidosis is any of a group of disparate conditions characterized by extracellular deposition of various insoluble proteins. These proteins may accumulate locally, causing relatively few symptoms, or widely, involving multiple organs and causing severe multiorgan failure. Amyloidosis can be primary or be secondary to various infectious, inflammatory, or malignant conditions. Rarely, it results from any of several inherited metabolic defects. Diagnosis is by biopsy of affected tissue. Treatment varies with the type of amyloidosis.

Amyloid deposits may be formed from at least 18 different proteins, including immunoglobulin fragments. Amyloid deposits are metabolically inert but interfere physically with organ structure and function. All stain positive with Congo red dye, stain pink with hematoxylin and eosin, and have apple-green birefringence under polarized light after Congo red staining. Amyloid deposits have a fibrillar, usually rigid, and nonbranching ultrastructure. They form a β-pleated sheet that can be seen by x-ray diffraction. In addition to the fibrillar amyloid protein, the deposits also contain serum amyloid P component and glycosaminoglycans. On gross inspection, affected organs appear waxy and translucent.

Etiology

There are 3 major systemic forms of amyloidosis: primary, secondary, and familial. Also, there are 2 major localized forms, Aβ (associated with Alzheimer's disease) and AIAPP (which occurs in the pancreas of patients with type 2 diabetes), as well as several miscellaneous forms (eg, $A\beta_2$-microglobulin associated with chronic hemodialysis).

Primary amyloidosis (AL): AL is a monoclonal plasma cell disorder in which the abnormal protein is an immunoglobulin, usually a light chain fragment (Bence Jones protein) but occasionally a heavy chain fragment (AH amyloidosis). These chains either have an aberrant structure or are processed abnormally so that some form insoluble deposits. Common sites for deposition include the skin, nerves, heart, GI tract (including tongue), kidneys, liver, spleen, and blood vessels. A mild plasmacytosis occurs in the bone marrow, which is suggestive of multiple myeloma, but most patients do not have true multiple myeloma (with lytic bone lesions, renal tubular casts, and anemia). However, about 10 to 20% of patients with multiple myeloma also develop amyloidosis.

Secondary amyloidosis (AA): This form can occur secondary to several infectious, inflammatory, and malignant (eg, renal cell carcinomas and others) conditions and is caused by the degradation of the acute-phase reactant serum amyloid A (SAA). Common causative infections include TB, bronchiectasis, osteomyelitis, and leprosy. Inflammatory conditions include RA, juvenile idiopathic arthritis (formerly juvenile RA), Crohn's disease, and familial Mediterranean fever. Inflammatory cytokines (eg, IL-1, tumor necrosis factor, IL-6) that are produced in these disorders cause increased hepatic production of the precursor protein SAA, which circulates in the serum.

AA amyloidosis shows a predilection for the spleen, liver, kidneys, adrenals, and lymph nodes. The liver, spleen, and kidneys are often enlarged, firm, and rubbery. Involvement of the heart and peripheral or autonomic nerves is rare. However, no organ system is spared, and vascular involvement may be widespread.

Familial amyloidosis: The familial form results from accumulation of a mutated version of a plasma protein (most commonly transthyretin [TTR], hence ATTR). Nearly all of the abnormal protein is produced by the liver. Over 80 mutations of the gene for TTR have been identified, all inherited in an autosomal dominant pattern.

Age at onset of symptoms is highly variable, ranging from the teens to the 70s. ATTR amyloidosis causes peripheral sensory and motor neuropathy, often with an autonomic neuropathy. Carpal tunnel syndrome is common. Later in the illness, cardiovascular and renal involvement occurs. Vitreous abnormalities may also develop.

Other very rare hereditary amyloidoses result from mutations of other physiologic proteins, including

apolipoprotein A-1, lysozyme, fibrinogen, gelsolin, and cystatin C. These amyloidoses have various systemic and localized effects.

A β_2-microglobulin (dialysis-related) amyloidosis: This form occurs in patients with chronic renal failure who have been on hemodialysis or peritoneal dialysis for long periods, usually > 8 yr. The amyloid deposits consist of β_2-microglobulin, a component of the class I major histocompatibility complex, which is normally cleared by the kidneys but cannot be removed by dialysis membranes. Deposits preferentially occur in and around bones and joints and in the carpal tunnel and have been found in the GI tract and in other organs.

A β-protein amyloidosis: This form occurs in patients with Alzheimer's disease. Although the exact role of amyloid deposits is unclear, the neuritic plaques characteristic of Alzheimer's disease contain amyloid deposits consisting of a β-protein fragment of β-amyloid precursor protein (a transmembrane glycoprotein). The β-protein fragment is sometimes complexed with apolipoprotein E. Within the plaques, nonfibrillar forms of the β protein are intermixed with fibrillar amyloid forms.

β-Protein amyloid deposition may also occur around cerebral blood vessels, which is thought to be a cause of nonhypertensive cerebral hemorrhage (cerebral amyloid angiopathy). The angiopathy may occur sporadically or as a hereditary syndrome (Dutch hereditary cerebral hemorrhage).

Symptoms and Signs

Symptoms and signs are nonspecific and relate to the organ or system affected. Symptoms in AA amyloidosis are often obscured by the underlying disease.

When the kidneys are affected, nephrotic syndrome is the most striking early manifestation. Initially, only slight proteinuria may occur; later, the distinctive symptom complex develops with anasarca, hypoproteinemia, and massive proteinuria.

Hepatic involvement causes painless hepatomegaly, which may be massive (liver weight > 7 kg). Except for occasional elevation of alkaline phosphatase, liver function tests remain normal. Jaundice is rare. Occasionally, portal hypertension develops, with resulting esophageal varices and ascites.

Cardiac involvement causes a restrictive cardiomyopathy, eventually leading to heart failure. Cardiomegaly and various degrees of heart block or arrhythmia may occur.

Peripheral neuropathy, with paresthesias of the fingers and toes, is a common presenting manifestation in AL and ATTR amyloidoses. Autonomic neuropathy may cause orthostatic hypotension, erectile dysfunction, sweating abnormalities, and GI motility disturbances.

Rheumatologic symptoms in patients with A β_2-microglobulin amyloidosis include carpal tunnel syndrome and chronic pain in the shoulder, wrist, and fingers. Pathologic fractures, particularly of the humerus and femur, may occur.

GI amyloid may cause motility abnormalities of the esophagus and small and large intestines. Gastric atony, malabsorption, bleeding, or pseudo-obstruction may also occur. Macroglossia is common in AL amyloidoses.

A firm, symmetric, nontender goiter resembling that found in Hashimoto's thyroiditis may result from amyloidosis of the thyroid gland. Lung involvement (mostly in AL amyloidosis) can be characterized by focal pulmonary nodules, tracheobronchial lesions, or diffuse alveolar deposits. In several hereditary amyloidoses, amyloid vitreous opacities and bilateral scalloped pupillary margins develop.

Diagnosis

• Biopsy

Amyloidosis is suspected clinically but can be diagnosed only by biopsy. Subcutaneous abdominal fat pad aspiration and biopsy of rectal mucosa are the best approaches. Other useful biopsy sites are the gingiva, skin, nerves, kidneys, and liver. Tissue sections are stained with Congo red dye and examined with a polarizing microscope for characteristic birefringence. Isotopically labeled serum AP (in which AP represents the pentagonal component of amyloid) can be used in a scintigraphic test to confirm the diagnosis.

Prognosis

Prognosis depends on the type of amyloidosis and the organ system involved. AL amyloidosis with multiple myeloma has the poorest prognosis: death within 1 yr is common. Untreated ATTR amyloidoses are fatal within 10 to 15 yr. Prognosis in other familial amyloidoses varies. In general, renal or cardiac involvement in patients with any type of amyloidosis is of particular concern.

Prognosis in AA amyloidosis depends on successful treatment of the underlying disorder, although rare patients undergo spontaneous regression of the amyloid deposits without such treatment.

Treatment

• Symptom relief

• Sometimes kidney transplantation

• Sometimes chemotherapy for AL amyloidosis

Management is generally symptomatic, although treatment of the underlying disorder can sometimes arrest amyloidosis. In patients with renal amyloid, kidney transplantation provides long-term survival comparable to that in other renal diseases, although mortality is higher in the early years. Amyloid ultimately recurs in a donor kidney, but several recipients have done very well and have survived up to 10 yr. Heart transplantation has been successful in carefully selected patients with AL amyloidosis and severe cardiac involvement.

Patients with AL amyloidosis are often treated with chemotherapy. A common protocol uses melphalan 0.075 mg/kg po bid and prednisone 0.2 mg/kg po qid. Melphalan with autologous stem cell transplantation achieves good short-term success and apparent cures in some cases.

In patients with ATTR amyloidosis, liver transplantation—which removes the site of synthesis of the mutant protein—is very effective.

For AA amyloidosis with familial Mediterranean fever, colchicine 0.6 mg po once/day or bid is effective. Underlying infections in patients with AA amyloidosis of infectious origin must be treated aggressively. Treatment of amyloid resulting from cancer (eg, renal cell carcinoma) is directed at the cancer.

Chapter 102. Carcinoid Tumors

Introduction

Carcinoid tumors develop from neuroendocrine cells in the GI tract (90%—see p. 191), pancreas, and pulmonary bronchi (see p. 2013). More than 95% of all GI carcinoids originate in only 3 sites: the appendix, ileum, and rectum. Although carcinoids are often benign or only locally invasive, those affecting the ileum and bronchus are frequently malignant.

Carcinoids can be endocrinologically inert or produce various hormones. The most common endocrinologic syndrome is carcinoid syndrome; however, most patients with carcinoids do not develop carcinoid syndrome. The likelihood that a tumor will be endocrinologically active varies with its site of origin, being highest for tumors originating in the ileum and proximal colon (40 to 50%). The likelihood is lower with bronchial carcinoids, lower still with appendiceal carcinoids, and essentially zero with rectal carcinoids.

Endocrinologically inert carcinoids are suspected because of their symptoms and signs (eg, pain, luminal bleeding, GI obstruction). They can be detected by angiography, CT, or MRI. Small-bowel carcinoids may exhibit filling defects or other abnormalities on barium x-rays. Definitive diagnosis is made histologically after biopsy or resection.

Endocrinologically active carcinoids are diagnosed and treated as described below.

Carcinoid Syndrome

Carcinoid syndrome develops in some people with carcinoid tumors and is characterized by cutaneous flushing, abdominal cramps, and diarrhea. Right-sided valvular heart disease may develop after several years. The syndrome results from vasoactive substances (including serotonin, bradykinin, histamine, prostaglandins, polypeptide hormones) secreted by the tumor, which is typically a metastatic intestinal carcinoid. Diagnosis is clinical and by demonstrating increased urinary 5-hydroxyindoleacetic acid. Tumor localization may require a radionuclide scan or laparotomy. Treatment of symptoms is with somatostatin or octreotide, but surgical removal is done where possible; chemotherapy may be used for malignant tumors.

Etiology

Endocrinologically active tumors of the diffuse peripheral endocrine or paracrine system produce various amines and polypeptides with corresponding symptoms and signs, including carcinoid syndrome. Carcinoid syndrome is usually due to endocrinologically active malignant tumors that develop from neuroendocrine cells (mostly in the ileum) and produce serotonin. It can, however, occur from tumors elsewhere in the GI tract (particularly the appendix and rectum), pancreas, bronchi, or, rarely, the gonads. Rarely, certain highly malignant tumors (eg, oat cell carcinoma of the lung, pancreatic islet cell carcinoma, medullary thyroid carcinoma) are responsible.

An intestinal carcinoid does not usually cause the syndrome unless hepatic metastases have occurred, because metabolic products released by the tumor are rapidly destroyed by blood and liver enzymes in the portal circulation (eg, serotonin by hepatic monoamine oxidase). Hepatic metastases, however, release metabolic products via the hepatic veins directly into the systemic circulation. Metabolic products released by primary pulmonary and ovarian carcinoids bypass the portal route and may similarly induce symptoms. Rare intestinal carcinoids with only intra-abdominal spread can drain directly into the systemic circulation or the lymphatics and cause symptoms.

Pathophysiology

Serotonin acts on smooth muscle to cause diarrhea, colic, and malabsorption. Histamine and bradykinin, through their vasodilator effects, cause flushing. The role of prostaglandins and various polypeptide hormones, which may be produced by paracrine cells, awaits further investigation; elevated human chorionic gonadotropin and pancreatic polypeptide levels are occasionally present with carcinoids.

Many patients develop right-sided endocardial fibrosis, leading to pulmonary stenosis and tricuspid regurgitation. Left heart lesions, which have been reported with bronchial carcinoids, are rare because serotonin is destroyed during passage through the lungs.

Symptoms and Signs

The most common (and often earliest) sign is an uncomfortable flushing, typically of the head and neck, often precipitated by emotional stress or the ingestion of food, hot beverages, or alcohol. Striking skin color changes may occur, ranging from pallor or erythema to a violaceous hue. Abdominal cramps with recurrent diarrhea occur and are often the patient's major complaint. Malabsorption syndrome may occur. Patients with valvular lesions may have a heart murmur. A few patients have asthmatic wheezing, and some have decreased libido and erectile dysfunction; pellagra develops rarely.

Diagnosis

• Urinary 5-hydroxyindoleacetic acid (5-HIAA)

Serotonin-secreting carcinoids are suspected based on their symptoms and signs. Diagnosis is confirmed by demonstrating increased urinary excretion of the serotonin metabolite 5-HIAA. To avoid false-positive results, clinicians do the test after the patient has abstained from serotonin-containing foods (eg, bananas, tomatoes, plums, avocados, pineapples, eggplant, walnuts) for 3 days. Certain drugs, including guaifenesin, methocarbamol, and phenothiazines, also interfere with the test and should be stopped temporarily before testing. On the 3rd day, a 24-h urine sample is collected for assay. Normal excretion of 5-HIAA is < 10 mg/day (< 52 µmol/day); in patients with carcinoid syndrome, excretion is usually > 50 mg/day (> 260 µmol/day).

Provocative tests with Ca gluconate, catecholamines, pentagastrin, or alcohol have been used to induce flushing. These tests may be helpful when the diagnosis is in doubt, but they must be done with care. Localization of the tumor involves the same techniques used to localize a nonfunctioning carcinoid (see p. 907) but may require extensive evaluation, sometimes including laparotomy. A scan with radionuclide-labeled somatostatin receptor ligand indium-111 pentetreotide or with iodine-123 metaiodobenzylguanidine may show metastases.

Other conditions that manifest with flushing and that could, therefore, be confused with carcinoid syndrome should be excluded. In patients in whom 5-HIAA excretion is not increased, disorders that involve systemic activation of mastocytes (eg, systemic mastocytosis with increased urinary levels of histamine metabolites and increased serum tryptase level) and idiopathic anaphylaxis may be responsible. Additional causes of flushing include menopause, ethanol ingestion, drugs such as niacin, and certain tumors (eg, vipomas, renal cell carcinoma, medullary thyroid carcinoma).

Prognosis

Despite metastatic disease, these tumors are slow growing, and survival of 10 to 15 yr is not unusual.

Treatment

• Surgical resection

• Octreotide for symptoms

Resection of primary lung carcinoids is often curative. For patients with hepatic metastases, surgery is only diagnostic or palliative, and radiation therapy is unsuccessful, in part because of the poor tolerance of normal hepatic tissue to radiation. No effective chemotherapeutic regimen has been established, but streptozocin with 5-fluorouracil is most widely used, sometimes with doxorubicin.

Certain symptoms, including flushing, have been relieved by somatostatin (which inhibits release of most hormones) without lowering urinary 5-HIAA or gastrin. Numerous studies have suggested good results

with octreotide, a long-acting analog of somatostatin. Octreotide is the drug of choice for controlling diarrhea and flushing. Case reports indicate that tamoxifen has been effective infrequently; leukocyte interferon (IFN-α) has temporarily relieved symptoms.

Flushing also can be treated with phenothiazines (eg, prochlorperazine 5 to 10 mg or chlorpromazine 25 to 50 mg po q 6 h). Histamine$_2$ blockers may also be used. Phentolamine (an α-blocker) 5 to 15 mg IV has prevented experimentally induced flushes. Corticosteroids (eg, prednisone 5 mg po q 6 h) may be useful for severe flushing caused by bronchial carcinoids.

Diarrhea may be controlled by codeine phosphate 15 mg po q 4 to 6 h, tincture of opium 0.6 mL po q 6 h, loperamide 4 mg po as a loading dose and 2 mg after each loose bowel to a maximum of 16 mg/day, diphenoxylate 5 mg po qid, or peripheral serotonin antagonists such as cyproheptadine 4 to 8 mg po q 6 h or methysergide 1 to 2 mg po qid.

Niacin and adequate protein intake are needed to prevent pellagra, because dietary tryptophan is diverted to serotonin by the tumor. Enzyme inhibitors that prevent the conversion of 5-hydroxytryptophan to serotonin include methyldopa 250 to 500 mg po q 6 h and phenoxybenzamine 10 mg/day.

Chapter 103. Multiple Endocrine Neoplasia Syndromes

Introduction

(Familial Endocrine Adenomatosis; Multiple Endocrine Adenomatosis)

The multiple endocrine neoplasia (MEN) syndromes comprise 3 genetically distinct familial diseases involving adenomatous hyperplasia and malignant tumors in several endocrine glands. Clinical features depend on the glandular elements involved.

Each syndrome is inherited as an autosomal dominant trait with a high degree of penetrance, variable expressivity, and production of seemingly unrelated effects by a single mutant gene. The specific mutation is not always known.

Symptoms and signs develop at any age. Proper management includes early identification of affected individuals within a kindred and surgical removal of the tumors when possible. Although these syndromes are generally considered clinically distinct, significant overlap exists (see Table 103-1).

Multiple Endocrine Neoplasia, Type 1

(Multiple Endocrine Adenomatosis, Type I; Wermer's Syndrome)

Multiple endocrine neoplasia, type 1 (MEN 1) is a hereditary syndrome characterized by tumors

[**Table 103-1.** Conditions Associated with Men Syndromes]

of the parathyroid glands, pancreatic islet cells, and pituitary gland. Clinical features most commonly include hyperparathyroidism and asymptomatic hypercalcemia. Genetic screening is used to detect carriers. Diagnosis is by hormonal and imaging tests. Tumors are surgically removed when possible.

MEN 1 is probably caused by an inactivating mutation of the tumor suppressor gene that encodes the transcription factor menin; many mutations of this gene may be responsible.

About 40% of MEN 1 cases involve tumors of all 3 affected glands—the parathyroids, pancreas, and pituitary. Almost any combination of the tumors and symptom complexes outlined below is possible. A patient with a MEN 1 gene mutation and one of the MEN 1 tumors is at risk of developing any of the other tumors later on. Age at onset ranges from 4 to 81 yr, but peak incidence occurs in the 20s in women and 30s in men. Women are affected twice as often as men.

Symptoms and Signs

The clinical features depend on the glandular elements affected (see Table 103-1).

Parathyroid: Hyperparathyroidism is present in ≥ 90% of patients. Asymptomatic hypercalcemia is the most common manifestation: about 25% of patients have evidence of nephrolithiasis or nephrocalcinosis. In contrast to sporadic cases of hyperparathyroidism, diffuse hyperplasia or multiple adenomas are more common than solitary adenomas.

Pancreas: Pancreatic islet cell tumors occur in 60 to 70% of patients. Tumors are usually multicentric. Multiple adenomas or diffuse islet cell hyperplasia commonly occurs; such tumors may arise from the small bowel rather than the pancreas. About 30% of tumors are malignant and have local or distant metastases. Malignant islet cell tumors due to MEN 1 syndrome often have a more benign course than do sporadically occurring malignant islet cell tumors.

About 40% of islet cell tumors originate from a β cell, secrete insulin (insulinoma), and can cause fasting hypoglycemia. β-Cell tumors are more common among patients < 40. About 60% of islet cell tumors

originate from non-β-cell elements and tend to occur in patients > 40. Non-β-cell tumors are somewhat more likely to be malignant.

Most islet cell tumors secrete pancreatic polypeptide, the clinical significance of which is unknown. Gastrin is secreted by many non-β-cell tumors (increased gastrin secretion in MEN 1 also often originates from the duodenum). Increased gastrin secretion increases gastric acid, which may inactivate pancreatic lipase, leading to diarrhea and steatorrhea. Increased gastrin secretion also leads to peptic ulcers in > 50% of MEN 1 patients. Usually the ulcers are multiple or atypical in location, and often bleed, perforate, or become obstructed. Peptic ulcer disease may be intractable and complicated (Zollinger-Ellison syndrome—see p. 200). Among patients presenting with Zollinger-Ellison syndrome, 20 to 60% have MEN 1.

A severe secretory diarrhea can develop and cause fluid and electrolyte depletion with non-β-cell tumors. This complex, referred to as the watery diarrhea, hypokalemia, and achlorhydria syndrome (WDHA; pancreatic cholera—see p. 201), has been ascribed to vasoactive intestinal polypeptide, although other intestinal hormones or secretagogues (including prostaglandins) may contribute. Hypersecretion of glucagon, somatostatin, chromogranin, or calcitonin, ectopic secretion of ACTH (causing Cushing's syndrome), and hypersecretion of growth hormone-releasing hormone (causing acromegaly) sometimes occur in non-β-cell tumors. All of these are rare in MEN 1.

Nonfunctioning pancreatic tumors also occur in patients with MEN 1 and may be the most common type of pancreatoduodenal tumor in MEN 1. The size of the nonfunctioning tumor correlates with risk of metastasis and death.

Pituitary: Pituitary tumors occur in 15 to 42% of MEN 1 patients. From 25 to 90% are prolactinomas. About 25% of pituitary tumors secrete growth hormone or growth hormone and prolactin. Excess prolactin may cause galactorrhea (see p. 770), and excess growth hormone causes acromegaly clinically indistinguishable from sporadically occurring acromegaly. About 3% of tumors secrete ACTH, causing Cushing's disease. Most of the remainder are nonfunctional. Local tumor expansion may cause visual disturbance, headache, and hypopituitarism. Pituitary tumors in MEN 1 patients appear to be larger and behave more aggressively than sporadic pituitary tumors.

Other manifestations: Adenomas and adenomatous hyperplasia of the thyroid and adrenal glands occurs occasionally in MEN 1 patients. Hormone secretion is rarely altered as a result, and the significance of these abnormalities is uncertain. Carcinoid tumors, particularly those derived from the embryologic foregut, occur in isolated cases. Multiple subcutaneous and visceral lipomas, angiofibromas, and collagenomas may also occur.

Diagnosis

• Clinical evaluation for other tumors of the triad

• Serum Ca, parathyroid hormone (PTH), gastrin, and prolactin levels

• Tumor localization with MRI, CT, or scintigraphy

• Genetic testing

Patients with tumors of the parathyroids, pancreas, or pituitary, particularly those with a family history of endocrinopathy, should undergo clinical screening for other tumors of MEN 1. Such screening includes the following:

• Asking about symptoms of peptic ulcer disease, diarrhea, nephrolithiasis, hypoglycemia, and hypopituitarism

• Examining for visual field defects, galactorrhea in women, and features of acromegaly and subcutaneous lipomas

• Measuring levels of serum Ca, intact PTH, gastrin, and prolactin

Additional laboratory or radiologic tests should be done if these screening tests suggest an endocrine abnormality related to MEN 1. An insulin-secreting β-cell tumor of the pancreas is diagnosed by detecting fasting hypoglycemia with an elevated plasma insulin level.

A gastrin-secreting non-β-cell tumor of the pancreas or duodenum is diagnosed by elevated basal plasma gastrin levels, an exaggerated gastrin response to infused Ca, and a paradoxical rise in gastrin level after infusion of secretin. An elevated basal level of pancreatic polypeptide or gastrin or an exaggerated response of these hormones to a standard meal may be the earliest sign of pancreatic involvement. CT or MRI can help localize tumors. Because these tumors are often small and difficult to localize, other imaging tests (eg, somatostatin receptor scintigraphy, endoscopic ultrasonography, intraoperative ultrasonography) may be necessary.

Acromegaly is diagnosed by elevated growth hormone levels that are not suppressed by glucose administration and by elevated levels of serum insulin-like growth factor 1.

In patients with 2 or more endocrine abnormalities related to MEN 1 who are not from a known MEN 1 kindred (index case), direct DNA sequencing of the MEN 1 gene identifies a specific mutation in 80 to 90%. If an index case is identified, 1st-degree relatives should consider genetic screening. Early presymptomatic screening of family members of MEN 1 patients has not been shown to reduce morbidity or mortality; annual clinical and biochemical screening may thus be preferable in this group.

Treatment

• Surgical excision when possible

• Drug management of hormone excess

Treatment of parathyroid and pituitary lesions is primarily surgical, although prolactinoma is usually managed with dopamine agonists. Islet cell tumors are more difficult to manage because the lesions are often small and difficult to find and multiple lesions are common. If a single tumor cannot be found, total pancreatectomy may be required for adequate control of hyperinsulinism. Diazoxide may be a useful adjunct in treating hypoglycemia. Streptozocin and other cytotoxic drugs may ameliorate symptoms by reducing tumor burden.

The treatment of gastrin-secreting non-β-cell tumors is complex. Localization and removal of the tumor should be attempted. If localization is impossible, a proton pump inhibitor frequently produces symptomatic relief from peptic ulcer disease. With the availability of these drugs, gastrectomy is rarely required.

Octreotide, a somatostatin analog, can block hormone secretion from nongastrin-secreting pancreatic tumors and is well tolerated, particularly if given as a long-acting preparation administered every 4 wk. Palliative treatments for metastatic pancreatic tumors include hepatic artery embolization and interferon alfa (in combination with octreotide).

Multiple Endocrine Neoplasia, Type 2A

(MEN 2; Multiple Endocrine Adenomatosis, Type 2; Sipple's Syndrome)

Multiple endocrine neoplasia, type 2A (MEN 2A) is a hereditary syndrome characterized by medullary carcinoma of the thyroid, pheochromocytoma, hyperparathyroidism, and occasionally cutaneous lichen amyloidosis. Clinical features depend on the glandular elements affected. Familial medullary thyroid carcinoma is a distinct variant of MEN 2A. Diagnosis involves genetic testing. Hormonal and imaging tests help locate the tumors, which are removed surgically when possible.

Mutations in the *RET* proto-oncogene on chromosome 10 have been identified in MEN 2A, MEN 2B, and

familial medullary thyroid carcinoma (FMTC). The RET protein is a receptor tyrosine kinase; MEN 2A and FMTC mutations result in activation of certain intracellular pathways.

Symptoms and Signs

Clinical features depend on the type of tumor present (Table 103-1).

Thyroid: Almost all patients have medullary thyroid carcinoma (MTC—see p. 790). The tumor usually develops during childhood and begins with thyroid parafollicular C-cell hyperplasia. Tumors are frequently multicentric.

Adrenal: Pheochromocytoma usually originates in the adrenal glands. Pheochromocytoma occurs in 40 to 50% of patients within a MEN 2A kindred, and in some kindreds pheochromocytoma accounts for 30% of deaths. In contrast to sporadic pheochromocytoma (see p. 801), the familial variety within MEN 2A begins with adrenal medullary hyperplasia and is multicentric and bilateral in > 50% of cases. Extra-adrenal pheochromocytomas are rare. Pheochromocytomas are almost always benign, but some tend to recur locally.

Pheochromocytomas that occur with MEN 2A (and 2B) usually produce epinephrine disproportionately to norepinephrine, in contrast to sporadic cases.

Hypertensive crisis secondary to pheochromocytoma is a common manifestation. Hypertension in MEN 2A patients with pheochromocytoma is more often paroxysmal than sustained, in contrast to the usual sporadic case. Patients with pheochromocytomas may have paroxysmal palpitations, anxiety, headaches, or sweating; many are asymptomatic.

Parathyroid: Ten to 20% of patients have evidence of hyperparathyroidism (which may be long-standing), with hypercalcemia, nephrolithiasis, nephrocalcinosis, or renal failure. Hyperparathyroidism frequently involves multiple glands as either diffuse hyperplasia or multiple adenomas, and mild abnormalities in parathyroid function may also be present in MEN 2A.

Other manifestations: Cutaneous lichen amyloidosis, a pruritic, scaly, papular skin lesion, located in the interscapular region or on extensor surfaces, occurs in some MEN 2A kindreds. Increased incidence of Hirschsprung's disease has been reported in children in at least one MEN 2A kindred.

Diagnosis

- Clinical suspicion
- Genetic testing
- Serum Ca, parathyroid hormone, and plasma free metanephrine or urinary catecholamine levels in affected patients
- Pheochromocytoma localization with MRI or CT

Many cases are identified during screening of family members of known cases. MEN 2A should also be suspected in patients with bilateral pheochromocytoma or at least 2 of its characteristic endocrine manifestations. The diagnosis can be confirmed with genetic testing. Although only 25% of MTC cases are familial, genetic testing of people with apparent sporadic MTC should be considered if patients are < 35 yr, tumors are bilateral or multicentric, or a family history is suspected.

Because pheochromocytoma may be asymptomatic, its exclusion may be difficult (see p. 802). The most sensitive tests are plasma free metanephrines and fractionated urinary catecholamines (particularly epinephrine). CT or MRI is useful in localizing the pheochromocytoma or establishing the presence of bilateral lesions.

Hyperparathyroidism is diagnosed by hypercalcemia, hypophosphatemia, and increased parathyroid

hormone level.

Screening: Genetic screening of family members of MEN 2A patients is now the diagnostic test of choice; the availability of such testing has made biochemical screening for early MTC largely obsolete. Among affected family members, annual screening for hyperparathyroidism and pheochromocytoma should begin in early childhood and continue indefinitely. Screening for hyperparathyroidism is with measurement of serum Ca. Screening for pheochromocytoma includes questions about symptoms, measurement of BP, and laboratory testing.

Treatment

• Surgical excision of identified tumors

• Prophylactic thyroidectomy

In patients presenting with pheochromocytoma and either MTC or hyperparathyroidism, the pheochromocytoma should be removed first; even if asymptomatic, it greatly increases risk of other surgeries. Once MTC has metastasized, chemotherapy and radiation therapy are largely ineffective in lengthening survival but may slow disease progression. Radioimmunotherapy has improved survival in initial studies.

Once genetic testing identifies a child as having a *RET* mutation, prophylactic thyroidectomy is recommended, generally when the child is between 4 and 6 yr; this potentially fatal condition can be cured or prevented by early thyroidectomy.

Multiple Endocrine Neoplasia, Type 2B

(MEN 3; Mucosal Neuroma Syndrome; Multiple Endocrine Adenomatosis, Type 2B)

Multiple endocrine neoplasia, type 2B (MEN 2B) is an autosomal dominant syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, multiple mucosal neuromas and intestinal ganglioneuromas, and often a marfanoid habitus. Symptoms depend on the glandular elements present. Diagnosis and treatment are the same as for MEN 2A.

Ninety-five percent of MEN 2B cases result from a single amino acid substitution in the RET protein. More than 50% are de novo mutations and thus seem to be sporadic rather than familial.

Symptoms and Signs

Symptoms and signs reflect the glandular abnormalities present (see Table 103-1). About 50% of patients have the complete syndrome with mucosal neuromas, pheochromocytomas, and medullary thyroid carcinoma (MTC). Fewer than 10% have neuromas and pheochromocytomas alone, whereas the remaining patients have neuromas and medullary carcinoma of the thyroid without pheochromocytoma.

Often, mucosal neuromas are the earliest sign, and they occur in most or all patients. Neuromas appear as small glistening bumps on the lips, tongue, and buccal mucosa. The eyelids, conjunctivae, and corneas also commonly develop neuromas. Thickened eyelids and diffusely hypertrophied lips are characteristic. GI abnormalities related to altered motility (constipation, diarrhea, and, occasionally, megacolon) are common and thought to result from diffuse intestinal ganglioneuromatosis. Patients may have a marfanoid habitus. Skeletal abnormalities of the spine (lordosis, kyphosis, scoliosis), pes cavus, and talipes equinovarus are common.

MTC and pheochromocytoma resemble the corresponding disorders in MEN 2A syndrome; both tend to be bilateral and multicentric. MTC, however, tends to be particularly aggressive in MEN 2B and may be present in very young children.

Although the neuromas, facial characteristics, and GI disorders are present at an early age, the syndrome may not be recognized until MTC or pheochromocytoma manifests in later life.

Diagnosis

• Clinical suspicion

• Genetic testing

• Plasma free metanephrine or urinary catecholamine levels

• Pheochromocytoma localization with MRI or CT

MEN 2B is suspected in patients with a family history of MEN 2B, pheochromocytoma, multiple mucosal neuromas, or MTC. Genetic testing is highly accurate and is done in 1st-degree relatives and any symptomatic family members of MEN 2B patients.

Pheochromocytoma may be suspected clinically and is confirmed by measuring plasma free metanephrines or urinary catecholamines (see p. 802). Laboratory testing for MTC may be done (see p. 790). MRI or CT is used to search for pheochromocytomas and MTC.

Treatment

• Surgical excision of identified tumors

• Prophylactic thyroidectomy

Affected patients should have total thyroidectomy as soon as the diagnosis is established. Pheochromocytoma, if present, should be removed before thyroidectomy is done. Gene carriers should undergo prophylactic thyroidectomy in infancy or early childhood.