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Endocrine disorders

Introduction

Together with the nervous system, the endocrine system regulates and integrates the body's metabolic activities. The endocrine system meets the nervous system at the hypothalamus. The hypothalamus, the main integrative center for the endocrine and autonomic nervous systems, controls the function of endocrine organs by neural and hormonal pathways. A hormone is a chemical transmitter released from specialized cells into the bloodstream, which carries it to specialized organ-receptor cells that respond to it.

Neural pathways connect the hypothalamus to the posterior pituitary, or neurohypophysis. Neural stimulation to the posterior pituitary provokes the secretion of two effector hormones: antidiuretic hormone (ADH) and oxytocin, and influences thyroid-stimulating hormone (TSH), corticotropin, prolactin, and gonadotropinreleasing hormone.

Hypothalamic control

The hypothalamus also exerts hormonal control at the anterior pituitary through releasing and inhibiting factors, which arrive by a portal system. Hypothalamic hormones stimulate the pituitary to release trophic hormones, such as corticotropin, TSH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and to release or inhibit effector hormones, such as the growth hormone and prolactin. In turn, secretion of trophic hormones stimulates the adrenal cortex, thyroid, and gonads. In a patient whose clinical condition suggests endocrine pathology, this

complex hormonal sequence requires careful evaluation at each level to identify the dysfunction; dysfunction may result from defects of releasing, trophic, or effector hormones or of the target tissue. Hyperthyroidism, for example, may result from an excess of thyrotropin-releasing hormone, TSH, or thyroid hormone.

In addition to hormonal and neural controls, a negative feedback system regulates the endocrine system. (See *Feedback mechanism of the endocrine system*.) The mechanism of feedback may be simple or complex. Simple feedback occurs when the level of one substance regulates secretion of a hormone. For example, low serum calcium levels stimulate parathyroid hormone (PTH) secretion; high serum calcium levels inhibit it. Complex feedback occurs through the hypothalamic-pituitary-target organ axis; for example, secretion of the hypothalamic corticotropin-releasing hormone (CRH) releases pituitary corticotropin, which, in turn, stimulates adrenal cortisol secretion. Subsequently, a rise in serum cortisol level inhibits corticotropin by decreasing CRH secretion. Steroid therapy disrupts the hypothalamic-pituitaryadrenal (HPA) axis by suppressing hypothalamic-pituitary secretion. Because abrupt withdrawal of steroids doesn't allow time for recovery of the HPA axis to stimulate cortisol secretion, it can induce a life-threatening adrenal crisis.

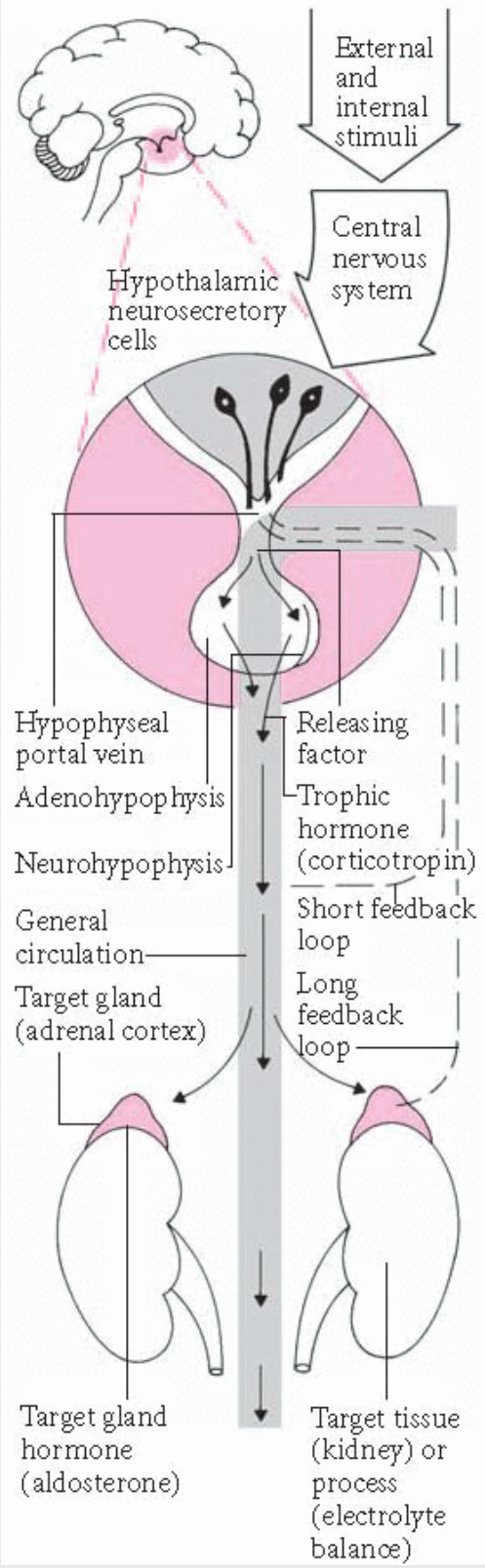
Hormonal effects

In response to the hypothalamus, the *posterior pituitary* secretes oxytocin and ADH. Oxytocin stimulates contraction of the uterus and is responsible for the milk letdown reflex in lactating females. ADH controls the concentration of body fluids by altering the permeability of the distal convoluted tubules and collecting ducts of the kidneys to conserve water. The secretion of ADH depends on plasma volume and osmolality as monitored by hypothalamic

neurons. Circulatory shock and severe hemorrhage are the most powerful stimulators of ADH; other stimulators include pain, emotional stress, trauma, morphine, tranquilizers, certain anesthetics, and positive-pressure breathing.

FEEDBACK MECHANISM OF THE ENDOCRINE SYSTEM

The hypothalamus receives regulatory information from its own circulating hormones (short feedback) and also from target glands (long feedback).


External and internal stimuli
Central nervous system
Hypothalamic neurosecretory cells
Hypophyseal portal vein
Adenohypophysis
Neurohypophysis
General circulation
Target gland (adrenal cortex)
Releasing factor
Trophic hormone (corticotropin)
Short feedback loop
Long feedback loop
Target gland hormone (aldosterone)
Target tissue (kidney) or process (electrolyte balance)

The syndrome of inappropriate ADH secretion is a disorder that produces hyponatremia with water overload. Generally, however, overhydration suppresses ADH secretion (as does alcohol). ADH deficiency causes diabetes insipidus, a condition of high urine output.

The *anterior pituitary* secretes prolactin, which stimulates milk production, and human growth hormone (hGH), which stimulates growth by increasing protein synthesis and fat mobilization and by decreasing carbohydrate utilization. Hyposecretion of hGH results in dwarfism; hypersecretion causes gigantism in children and acromegaly in adults.

The *thyroid gland* secretes the iodinated hormones thyroxine and triiodothyronine. Thyroid hormones, necessary for normal growth and development, act on many tissues to increase metabolic activity and protein synthesis. Deficiency of thyroid hormone causes varying degrees of hypothyroidism, from a mild, clinically insignificant form to life-threatening myxedema coma. Congenital hypothyroidism causes cretinism. Hypersecretion causes hyperthyroidism and, in extreme cases, thyrotoxic crisis. Excessive secretion of TSH causes thyroid gland hyperplasia, resulting in goiter.

The *parathyroid glands* secrete PTH, which regulates calcium and phosphate metabolism. PTH elevates serum calcium levels by stimulating resorption of calcium and phosphate from bone, reabsorption of calcium and excretion of phosphate by the kidneys and, by combined action with vitamin D, absorption of calcium and phosphate from the GI tract. PTH also stimulates conversion of vitamin D to its metabolically active form. Thyrocalcitonin, a secretion from the thyroid, opposes the effect of PTH and therefore decreases serum calcium levels. Hyperparathyroidism results in hypercalcemia, and hypoparathyroidism causes hypocalcemia. Altered calcium levels may also result from nonendocrine causes such as metastatic bone disease or nutritional vitamin D deficiency.

The *endocrine* part of the *pancreas* produces glucagon from the alpha cells and insulin from the beta cells. Glucagon, the hormone of the fasting state, releases stored glucose to raise the blood glucose level. Insulin, the hormone of the nourished state, facilitates glucose transport, promotes glucose storage, stimulates protein synthesis, and enhances free fatty acid uptake and storage. Absolute or relative insulin

deficiency causes diabetes mellitus. Insulin excess can result from an insulinoma (a tumor of the beta cells).

ELDER TIP

A common and important endocrine change in older people is a decreased ability to tolerate stress, as demonstrated by glucose metabolism. Normally, fasting blood glucose levels aren't significantly different in young and old adults. However, when stress stimulates an older person's pancreas, the blood glucose concentration increases and remains elevated longer than in a young adult.

The *adrenal cortex* secretes mineralocorticoids, glucocorticoids, and sex steroids. Aldosterone, a mineralocorticoid, regulates the reabsorption of sodium and the excretion of potassium by the kidneys. Although affected by corticotropin, aldosterone is regulated by angiotensin II, which in turn, is regulated by renin and plasma volume. Together, aldosterone, angiotensin, and renin may be implicated in the pathogenesis of hypertension. An excess of aldosterone (aldosteronism) can result primarily from hyperplasia or from adrenal adenoma or secondarily from many conditions, including heart failure and cirrhosis.

Cortisol, a glucocorticoid, stimulates gluconeogenesis, increases protein breakdown and free fatty acid mobilization, suppresses the immune response, and provides for an appropriate response to stress. Hyperactivity of the adrenal cortex results in Cushing's syndrome; hypoactivity of the adrenal cortex causes Addison's disease and, in extreme cases, adrenal crisis. Adrenogenital syndromes may result from overproduction of sex steroids.

The *adrenal medulla* is an aggregate of nervous tissue that produces the catecholamines

epinephrine and norepinephrine, both of which cause vasoconstriction. Epinephrine also causes the fight-or-flight response—dilation of bronchioles and increased blood pressure, blood glucose levels, and heart rate. Pheochromocytoma, a tumor of the adrenal medulla, causes

hypersecretion of catecholamines and results in characteristic sustained or paroxysmal hypertension.

The *testes* synthesize and secrete testosterone in response to gonadotropic hormones, especially LH, from the anterior pituitary gland; spermatogenesis occurs in response to FSH. The *ovaries* produce sex steroid hormones, primarily estrogen and progesterone, in response to LH and FSH.

Endocrine dysfunction

Chronic endocrine abnormalities are common health problems. For example, deficiencies of cortisol, thyroid hormone, or insulin may require lifelong hormone replacement for survival. Consequently, these conditions make special demands on your skills during ongoing patient assessment, acute illness, and patient teaching.

Common dysfunctions of the endocrine system are classified as hypofunction and hyperfunction, inflammation, and tumor. The source of hypofunction and hyperfunction may originate in the hypothalamus or in the pituitary or effector glands. Inflammation may be acute or subacute, as in thyroiditis, but is usually chronic, commonly resulting in glandular hypofunction. Tumors can occur within a gland— as in thyroid cancer—or adrenal pheochromocytoma —or in other areas, resulting in ectopic hormone production. Certain lung tumors, for example, secrete ADH, PTH, or structurally similar substances that have the same effects on target tissues.

The study of endocrine function focuses on measuring the level or effect of a hormone. Radioimmunoassay, for example, measures insulin levels; a fasting blood glucose test measures insulin's effects. Sophisticated techniques of hormone measurement have improved diagnosis of endocrine disorders.

Diagnostic tests confirm endocrine disorders but clinical data usually provide the first clues. Nursing assessment can reveal such signs and symptoms as excessive or delayed growth, wasting, weakness, polydipsia, polyuria, and mental changes. The quality and distribution of hair, skin pigmentation, and the distribution of body fat are also significant.

Nurses are also responsible for patient preparation, including instruction and support during testing, and for specimen collection, particularly of timed blood and urine specimens.

PITUITARY GLAND

Hypopituitarism

Hypopituitarism, which includes panhypopituitarism and dwarfism, is a complex syndrome marked by metabolic dysfunction, sexual immaturity, and growth retardation (when it occurs in childhood), resulting from a deficiency of the hormones secreted by the anterior pituitary gland. Panhypopituitarism refers to a generalized condition caused by partial or total failure of the anterior pituitary's vital hormones —corticotropin, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), human growth hormone (hGH), and prolactin —plus the posterior pituitary hormone, antidiuretic hormone. Partial hypopituitarism and complete hypopituitarism occur in adults and children; in children, these diseases may cause dwarfism and delayed puberty. The prognosis may be good with adequate replacement therapy and correction of the underlying causes.

Causes and incidence

The most common cause of primary hypopituitarism in adults is a tumor. Other causes include congenital defects (hypoplasia or aplasia of the pituitary gland); pituitary infarction (most often from postpartum hemorrhage); or partial or total hypophysectomy by surgery, irradiation, or chemical agents; and, rarely, granulomatous disease (tuberculosis, for example). Occasionally, hypopituitarism may have no identifiable cause, or it may be related to

autoimmune destruction of the gland. Secondary hypopituitarism stems from a deficiency of releasing hormones produced by the hypothalamus—either idiopathic or possibly resulting from infection, trauma, or a tumor.

Primary hypopituitarism usually develops in a predictable pattern of hormonal failures. It generally starts with hypogonadism from

gonadotropin failure (decreased FSH and LH levels). In adults, it causes cessation of menses in females and impotence in men. Growth hormone (GH) deficiency follows; in children, this causes short stature, delayed growth, and delayed puberty. In adults, it causes osteoporosis, decreased lean-to-fat body mass index, adverse lipid changes, and subtle emotional dysphoria and lethargy. Subsequent failure of thyrotropin (decreased TSH levels) causes hypothyroidism; finally, adrenocorticotropic failure (decreased corticotropin levels) results in adrenal insufficiency. However, when hypopituitarism follows surgical ablation or trauma, the pattern of hormonal events may not necessarily follow this sequence. Sometimes, damage to the hypothalamus or neurohypophysis from one of the above leads to diabetes insipidus. Hypopituitarism may develop years after pituitary radiation treatment.

Signs and symptoms

Clinical features of hypopituitarism develop slowly and vary with the severity of the disorder and the number of deficient hormones. Signs and symptoms of hypopituitarism in adults may include gonadal failure (secondary amenorrhea, impotence, infertility, decreased libido), diabetes insipidus, hypothyroidism (fatigue, lethargy, sensitivity to cold, menstrual disturbances), and adrenocortical insufficiency (hypoglycemia, anorexia, nausea, abdominal pain, orthostatic hypotension).

Postpartum necrosis of the pituitary (Sheehan's syndrome) characteristically causes failure of lactation, menstruation, and growth of pubic and axillary hair; and symptoms of thyroid and adrenocortical failure.

In children, hypopituitarism causes retarded growth or delayed puberty. Dwarfism usually isn't apparent at birth but early signs begin to appear during the first few months of life; by age 6 months, growth retardation is obvious. Although these children generally enjoy good health, pituitary dwarfism may cause chubbiness due to fat deposits in the lower trunk, delayed secondary tooth eruption and, possibly, hypoglycemia. Growth continues at less than half the normal rate—sometimes extending into the patient's 20s or 30s—to an average height of 4′ (122 cm), with normal proportions.

When hypopituitarism strikes before puberty, it prevents development of secondary sex characteristics (including facial and body hair). In males, it produces undersized testes, penis, and prostate gland; absent or minimal libido; and the inability to initiate and maintain an erection. In females, it usually causes immature development of the breasts, sparse or absent pubic and axillary hair, and primary amenorrhea.

Panhypopituitarism may induce a host of mental and physiologic abnormalities, including lethargy, psychosis, orthostatic hypotension, bradycardia, anemia, and anorexia. However, clinical manifestations of hormonal deficiencies resulting from pituitary destruction don't become apparent until 75% of the gland is destroyed. Total loss of all hormones released by the anterior pituitary is fatal unless treated.

Neurologic signs associated with hypopituitarism and produced by pituitary tumors include headache, bilateral temporal hemianopia, loss of visual acuity and, possibly, blindness. Acute hypopituitarism resulting from surgery or infection is often associated with fever, hypotension, vomiting, and hypoglycemia—all characteristic of adrenal insufficiency.

Diagnosis

In suspected hypopituitarism, evaluation must confirm hormonal deficiency due to impairment or destruction of the anterior pituitary gland and rule out disease of the target organs (adrenals, gonads, and thyroid) or the hypothalamus. Low serum levels of thyroxine (T_4), for example, indicate diminished thyroid gland function, but further tests are necessary to identify the source of this dysfunction as the thyroid, pituitary, or hypothalamus.

Serum insulin-like growth factor 1 (IGF-1) is decreased. Cranial computed tomography (CT) scan or magnetic resonance imaging (MRI) may reveal a tumor or abnormal mass in the pituitary gland or the hypothalamus. Radioimmunoassay showing decreased plasma levels of some or all pituitary hormones, accompanied by end-organ hypofunction, suggests pituitary failure, and eliminates target gland disease. Failure of thyrotropin-releasing hormone administration to increase TSH or prolactin concentrations rules out hypothalamic dysfunction as the cause of hormonal deficiency.

Provocative tests are helpful in pinpointing the source of low cortisol levels. Oral metyrapone blocks cortisol synthesis, which should stimulate pituitary secretion of corticotropin and the adrenal precursors of cortisol, measured in urine as hydroxycorticosteroids. Insulin-induced hypoglycemia also stimulates corticotropin secretion. Persistently low levels of corticotropin indicate pituitary or hypothalamic failure. These tests require careful medical supervision because they may precipitate an adrenal crisis.

CONFIRMING DIAGNOSIS

Diagnosis of hypopituitarism requires measurement of GH levels in the blood after administration of regular insulin (inducing hypoglycemia) or levodopa (causing hypotension). These drugs should provoke increased secretion of GH. Persistently low GH levels, despite provocative testing, confirm GH deficiency. CT scan, MRI, or cerebral angiography confirms the presence of intrasellar or extrasellar tumors.

Treatment

Replacement of hormones secreted by the target glands is the most effective treatment for hypopituitarism. Hormone replacement therapy includes cortisol, T_4, and androgen or cyclic estrogen. Prolactin need not be replaced. The patient of reproductive age may benefit from administration of FSH and human chorionic gonadotropin to boost fertility. GH replacement is recommended for adults as well as children. Replacement is done by administering daily subcutaneous injections of one of several recombinant deoxyribonucleic acid (DNA) GHs, accompanied by follow-up of serum IGF-1 levels. Lean body mass increases, whereas adipose tissue—particularly in the abdomen—decreases. Risk of cardiovascular disease and osteoporosis also decrease with treatment. Many patients also notice an improved sense of well-being.

Somatrem, which is identical to hGH but is the product of recombinant DNA technology, has replaced GHs derived from human sources. It's effective for treating dwarfism and stimulates growth increases as great

as 4′ to 6′ (10 to 15 cm) in the first year of treatment. The growth rate tapers off in subsequent years. After pubertal changes have occurred, the effects of somatrem therapy are limited. Occasionally, a child becomes unresponsive to somatrem therapy, even with larger doses, perhaps because antibodies have formed against it. In such refractory patients, small doses of androgen may again stimulate growth but extreme caution is necessary to prevent premature closure of the epiphyses. Children with hypopituitarism may also need replacement of adrenal and thyroid hormones and, as they approach puberty, sex hormones.

Special considerations

Caring for patients with hypopituitarism requires an understanding of hormonal effects and skilled physical and psychological support.

- Monitor the results of all laboratory tests for hormonal deficiencies, and know what they mean. Until hormone replacement therapy is complete, check for signs of thyroid deficiency (increasing lethargy, slow pulse, constipation, dry hair and skin), adrenal deficiency (weakness, orthostatic hypotension, hypoglycemia, fatigue, and weight loss), and gonadotropin deficiency (decreased libido, lethargy, and apathy).
- Watch for anorexia in the patient with panhypopituitarism. Help plan a menu containing favorite foods—ideally, high-calorie foods. Monitor for weight loss or gain.
- If the patient has trouble sleeping, encourage exercise during the day.
- Record temperature, blood pressure, and heart rate every 4 to 8 hours. Check eyelids, nail beds, and skin for pallor, which indicates anemia.
- Prevent infection by giving meticulous skin care. Because the patient's skin is probably dry, use oil or lotion instead of soap. If body temperature is low, provide additional clothing and covers, as needed, to keep the patient warm.
- Darken the room if the patient has a tumor that's causing headaches and visual disturbances. Help with any activity that requires good

vision such as reading the menu. The patient with bilateral hemianopia has impaired peripheral vision, so be sure to stand where he can see you, and advise the family to do the same.

- During insulin testing, monitor closely for signs of hypoglycemia (initially, slow cerebration, tachycardia, diaphoresis, and nervousness, progressing to seizures). Keep dextrose 50% in water available for I.V. administration to correct hypoglycemia rapidly.
- To prevent orthostatic hypotension, be sure to keep the patient supine during levodopa testing.
- Instruct the patient to wear a medical identification bracelet. Teach him and his family members how to administer steroids rectally or parenterally in case of an emergency.
- Refer the family of a child with dwarfism to the appropriate community resources for psychological counseling because the emotional stress caused by this disorder increases as the child becomes more aware of his condition.

Hyperpituitarism

Hyperpituitarism, also called acromegaly and gigantism, are chronic, progressive diseases marked by hormonal dysfunction and startling skeletal overgrowth. Although the prognosis depends on the causative factor, these disorders usually reduce life expectancy unless treated in a timely fashion.

Acromegaly occurs after epiphyseal closure, causing bone thickening and transverse bone growth and visceromegaly.

Gigantism begins before epiphyseal closure and causes proportional overgrowth of all body tissues. As the disease progresses, loss of other trophic hormones, such as thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and corticotropin, may cause dysfunction of the target organs.

Causes and incidence

Typically, oversecretion of human growth hormone (hGH) produces changes throughout the body, resulting in acromegaly and, when

oversecretion occurs before puberty, gigantism. Eosinophilic or mixed-cell adenomas of the anterior pituitary gland may cause this oversecretion but the etiology of the tumors themselves remains unclear. Occasionally, hGH levels are elevated in more than one family member, which suggests the possibility of a genetic cause.

The earliest clinical manifestations of acromegaly include soft-tissue swelling of the extremities and coarsening of facial features. This rare form of hyperpituitarism occurs equally among males and females, usually between ages 30 and 50. Annually, it affects 3 to 4 people per every million.

In gigantism, proportional overgrowth of all body tissues causes remarkable height increases of as much as 6′ (15 cm) per year. Gigantism affects infants and children, causing them to attain as much as three times the normal height for their age. As adults, they may ultimately reach a height of more than 80′ (203 cm). Gigantism is rare; there have only been 100 reported cases.

Complications

- *Increased hGH secretion*—arthritis, carpal tunnel syndrome, osteoporosis, kyphosis, hypertension, arterosclerosis, heart enlargement, heart failure
- *Acromegaly*—blindness, neurologic disturbances
- *Acromegaly and gigantism*—glucose intolerance, diabetes mellitus

Signs and symptoms

Acromegaly develops slowly and typically produces diaphoresis, oily skin, hypermetabolism, and hypertrichosis. Severe headache, central nervous system impairment, bitemporal hemianopia, loss of visual acuity, and blindness may result from the

intrasellar tumor compressing the optic chiasm or nerves.

Hypersecretion of hGH produces cartilaginous and connective tissue overgrowth, resulting in a characteristic hulking appearance, with an enlarged supraorbital ridge and thickened ears and nose. Prognathism, projection of the jaw, becomes marked and may interfere with chewing.

Laryngeal hypertrophy, paranasal sinus enlargement, and thickening of the tongue cause the voice to sound deep and hollow. Distal phalanges display an arrowhead appearance on X-rays, and the fingers are thickened. Irritability, hostility, and various psychological disturbances may occur.

Prolonged effects of excessive hGH secretion include bowlegs, barrel chest, arthritis, osteoporosis, kyphosis, hypertension, and arteriosclerosis. Both gigantism and acromegaly may also cause signs of glucose intolerance and clinically apparent diabetes mellitus because of the insulinantagonistic character of hGH. If acromegaly is left untreated, the patient is at risk for premature cardiovascular disease, colon polyps, and colon cancer.

Gigantism develops abruptly, producing some of the same skeletal abnormalities seen in acromegaly. As the disease progresses, the pituitary tumor enlarges and invades normal tissue, resulting in the loss of other trophic hormones, such as thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and corticotropin, thus causing the target organ to stop functioning.

Diagnosis

Plasma hGH and somatomedin-C levels measured by radioimmunoassay typically are elevated. Because hGH secretion is pulsatile, the results of random sampling may be misleading. The glucose suppression test offers more reliable information. Glucose normally suppresses hGH secretion; therefore, a glucose infusion that doesn't suppress the hormone level to below the accepted normal value of 5 nanograms (ng)/ml, when combined with characteristic clinical features, strongly suggests hyperpituitarism. The level of insulin-like growth factor 1 (IGF-1) is high.

In addition, skull X-rays, computed tomography scan, arteriography, and magnetic resonance imaging determine the presence and extent of the pituitary lesion. Bone X-rays showing a thickening of the cranium (especially of frontal, occipital, and parietal bones) and of the long bones, as well as osteoarthritis in the spine, support this diagnosis.

Treatment

Treatment aims to curb overproduction of hGH through removal of the underlying tumor by cranial or transsphenoidal hypophysectomy or pituitary radiation therapy. In acromegaly, surgery is mandatory when a tumor causes blindness or other severe neurologic disturbances. Postoperative therapy often requires replacement of thyroid, cortisone, and gonadal hormones. Adjunctive treatment may include administration of bromocriptine or cabergoline and octreotide and postoperative conventional proton beam radiation, which inhibit hGH synthesis. The therapeutic goal is to reach and maintain hGH levels less than 1 ng/ml and IGF-1 to normal range for age and gender, because at that level, life expectancy is restored to that of age-matched controls.

Special considerations

The extreme body changes characteristic of this disorder can cause severe psychological stress; therefore, emotional support to help the patient cope with his altered body image is an integral part of patient care.

- Assess for skeletal manifestations, such as arthritis of the hands and osteoarthritis of the spine. Administer medications as ordered. To promote maximum joint mobility, perform or assist with range-of-motion exercises.
- Evaluate muscle weakness, especially in the patient with late-stage acromegaly. Check the strength of his handclasp. If it's very weak, help with tasks such as cutting food.
- Keep the skin dry. Avoid using an oily lotion because the skin is already oily.
- Test blood for glucose. Check for signs of hyperglycemia (fatigue, polyuria, and polydipsia).
- Be aware that the tumor may cause visual problems. If the patient has hemianopia, stand where he can see you. Remember, this disease can also cause inexplicable mood changes. Reassure the family that these mood changes result from the disease and can be modified with treatment.

- Before surgery, reinforce what the surgeon has told the patient, and try to allay the patient's fear with a clear and honest explanation of the scheduled operation.

PEDIATRIC TIP

If the patient is a child, explain to his parents that such surgery prevents permanent soft-tissue deformities but won't correct bone changes that have already taken place. Arrange for counseling, if necessary, to help the child and his parents cope with these permanent defects.

ALERT

After surgery, diligently monitor vital signs and neurologic status. Immediately report increased urinary output lasting over 2 hours, alteration in level of consciousness, unequal pupil size, changes in visual acuity, vomiting, falling pulse rate, or rising blood pressure. These changes may signal an increase in intracranial pressure due to intracranial bleeding or cerebral edema.

- Check blood glucose level often. Remember, hGH levels usually fall rapidly after surgery, removing an insulin-antagonist effect in many patients and possibly precipitating hypoglycemia. Measure intake and output hourly, and report large increases. Transient diabetes insipidus, which sometimes occurs after surgery for hyperpituitarism, can cause such increases in urine output.
- If the transsphenoidal approach is used, a large nasal packing is kept in place for several days. Because the patient must breathe through his mouth, give good mouth care. Pay special attention to the mucous membranes—which usually become dry—and the incision site under the upper lip, at the top of the gum line. The surgical site is packed with a piece of tissue generally taken from a midthigh donor site. Watch for cerebrospinal fluid leaks from the packed site, which may necessitate additional surgery to repair the leak. Look for increased external nasal drainage or drainage into the nasopharynx.

- Encourage the patient to walk as soon as possible after surgery.
- Before discharge, emphasize the importance of continuing hormone replacement therapy, if ordered. Make sure the patient and his family understand which hormones are to be taken and why as well as the correct times and dosages. Warn against stopping the hormones suddenly.
- Advise the patient to wear a medical identification bracelet at all times and to bring his hormone replacement schedule with him whenever he returns to the health care facility.
- Instruct the patient to have follow-up examinations for the rest of his life because a slight chance exists that the tumor that caused his condition may recur.

Diabetes insipidus

Diabetes insipidus (also called *pituitary diabetes insipidus*) is a disorder of water metabolism resulting from a deficiency of circulating vasopressin (also called *antidiuretic hormone* [ADH]). It's characterized by excessive fluid intake and hypotonic polyuria. The disorder may start in childhood or early adulthood (the median age of onset is 21) and is more common in males than in females. Incidence is slightly higher today than in the past. In uncomplicated diabetes insipidus, the prognosis is good with adequate water replacement and replacement of ADH by tablet or nasal spray, and patients usually lead normal lives.

Causes and incidence

Diabetes insipidus results centrally from intracranial neoplastic or metastatic lesions, hypophysectomy or other neurosurgery, a skull fracture, or head trauma that damages the neurohypophyseal structures. It can also result nephrogenically from infection, granulomatous disease, and vascular lesions; it may be idiopathic and, rarely, familial. (*Note:* Pituitary diabetes insipidus shouldn't be confused with nephrogenic diabetes insipidus, a rare congenital disturbance of water metabolism that results from renal tubular resistance to vasopressin.)

Normally, the hypothalamus synthesizes vasopressin. The posterior pituitary gland (or neurohypophysis) stores vasopressin and releases it into general circulation, where it causes the kidneys to reabsorb water by making the distal tubules and collecting duct cells water-permeable. The absence of vasopressin in diabetes insipidus allows the filtered water to be excreted in the urine instead of being reabsorbed.

Nephrogenic diabetes insipidus involves a defect in the parts of the kidneys that reabsorb water back into the bloodstream. It occurs less commonly than central diabetes insipidus. Nephrogenic diabetes insipidus may occur as an inherited disorder in which boys receive the abnormal gene that causes the disease on the × chromosome from their mothers. Nephrogenic diabetes insipidus may also be caused by diseases of the kidney (such as polycystic kidney disease) and the effects of certain drugs (such as lithium and amphotericin B) and as a result of hypercalcemia and hypokalemia.

Diabetes insipidus is rare, affecting 1 in 25,000 people. Males and females are affected equally.

Complications

- Hypovolemia
- Hyperosmolality
- Circulatory collapse
- Loss of consciousness
- Central nervous system damage

Signs and symptoms

The patient's history typically shows an abrupt onset of extreme polyuria (usually 4 to 16 L/day of dilute urine but sometimes as much as 30 L/day). As a result, the patient is extremely thirsty and drinks great quantities of water to compensate for the body's water loss. This disorder may also result in nocturia. In severe cases, it may lead to extreme fatigue from inadequate rest caused by frequent voiding and excessive thirst.

Other characteristic features of diabetes insipidus include signs and symptoms of dehydration (poor tissue turgor, dry mucous membranes, constipation, muscle weakness, dizziness, and hypotension). These symptoms usually begin abruptly, commonly appearing within 1 to 2 days after a basal skull fracture, a stroke, or surgery. Relieving cerebral edema or increased intracranial pressure may cause all of these symptoms to subside just as rapidly as they began.

Diagnosis

Urinalysis reveals almost colorless urine of low osmolality (50 to 200 mOsm/kg, less than that of plasma) and low specific gravity (less than 1.005).

CONFIRMING DIAGNOSIS

Diagnosis requires evidence of vasopressin deficiency, resulting in the kidneys' inability to concentrate urine during a water deprivation test.

In this test, after baseline vital signs, weight, and urine and plasma osmolalities are obtained, the patient is deprived of fluids and observed to make sure he doesn't drink anything surreptitiously. Hourly measurements then record the total volume of urine output, body weight, urine osmolality or specific gravity, and plasma osmolality. Throughout the test, blood pressure and pulse rate must be monitored for signs of orthostatic hypotension. Fluid deprivation continues until the patient loses 3% of his body weight (indicating severe dehydration). When urine osmolality stops increasing in three consecutive hourly specimens, patients receive 5 units of aqueous vasopressin subcutaneously.

Hourly measurements of urine volume and specific gravity continue after subcutaneous injection of aqueous vasopressin. Patients with pituitary diabetes insipidus respond to exogenous vasopressin with decreased urine output and increased specific gravity. Patients with nephrogenic diabetes insipidus show no response to vasopressin.

Treatment

Mild cases require no treatment other than fluid intake to replace fluid lost. Until the cause of more severe cases of diabetes insipidus can be identified and eliminated, administration of various forms of vasopressin or of a vasopressin stimulant can

control fluid balance and prevent dehydration. Vasopressin injection is an aqueous preparation that's administered subcutaneously or I.M. several times a day because it's effective for only 2 to 6 hours; this form of the drug is used in acute disease and as a diagnostic agent.

Desmopressin acetate (DDAVP) can be given by nasal spray that's absorbed through the mucous membranes, or by injection given subcutaneously or I.V.; this drug is effective for 8 to 20 hours, depending on the dosage. It's also available in tablet form, to be given at bedtime or in divided doses. Hydrochlorothiazide can be used in both central and nephrogenic diabetes insipidus. Indomethacin and amiloride are also used for nephrogenic diabetes insipidus. If nephrogenic diabetes insipidus is caused by medication (such as lithium [Eskalith]), stopping the medicine leads to kidney recovery.

Special considerations

Patient care includes monitoring symptoms to ensure that fluid balance is restored and maintained.

- Record fluid intake and output carefully. Maintain fluid intake that's adequate to prevent severe dehydration. Watch for signs of hypovolemic shock, and monitor blood pressure and heart and respiratory rates regularly, especially during the water deprivation test. Check the patient's weight daily.
- If the patient is dizzy or has muscle weakness, keep the side rails up and assist him with walking.
- Monitor urine specific gravity between doses. Watch for a decrease in specific gravity accompanied by increasing urine output, indicating the recurrence of polyuria and necessitating administration of the next dose of medication or a dosage increase.
- Institute safety precautions for the patient who's dizzy or who has muscle weakness.

- If constipation develops, add more highfiber foods and fruit juices to the patient's diet. If necessary, obtain an order for a mild laxative such as milk of magnesia.
- Provide meticulous skin and mouth care; apply petroleum jelly, as needed, to cracked or sore lips.
- Before discharge, teach the patient how to monitor intake and output.
- Instruct the patient to administer desmopressin by nasal spray only after the onset of polyuria—not before—to prevent excess fluid retention and water intoxication.
- Tell the patient to report weight gain, which may indicate that his medication dosage is too high. Recurrence of polyuria, as reflected on the intake and output sheet, indicates that the dosage is too low.
- Teach the parents of a child with diabetes insipidus about normal growth and development. Discuss how their child may differ from others at his developmental stage.
- Encourage the parents to help identify the child's strengths and to use them in developing coping strategies.
- Refer the family for counseling if necessary.
- Advise the patient with diabetes insipidus to wear a medical identification bracelet and to carry his medication with him at all times.

THYROID GLAND

Hypothyroidism in adults

Hypothyroidism, a state of low serum thyroid hormone, results from hypothalamic, pituitary, or thyroid insufficiency. The disorder can progress to life-threatening myxedema coma.

Causes and incidence

Hypothyroidism results from inadequate production of thyroid hormone—usually because of dysfunction of the thyroid gland due to surgery (thyroidectomy), irradiation therapy (particularly with ^{131}I),

inflammation, chronic autoimmune thyroiditis (Hashimoto's disease) or, rarely, conditions such as amyloidosis and sarcoidosis. It may also result from pituitary failure to produce thyroid-stimulating hormone (TSH), hypothalamic failure to produce

thyrotropin-releasing hormone, inborn errors of thyroid hormone synthesis, the inability to synthesize thyroid hormone because of iodine deficiency (usually dietary), or the use of antithyroid medications such as propylthiouracil. In patients with hypothyroidism, infection, exposure to cold, and sedatives may precipitate myxedema coma.

Hypothyroidism is more prevalent in females than males, and frequency increases with age; in the United States, incidence is rising significantly in people ages 40 to 50.

Complications

- *Cardiovascular*—arteriosclerosis, ischemic heart disease, poor peripheral circulation, heart enlargement, heart failure, and pleural and pericardial effusion
- *Gastrointestinal*—achlorhydria, pernicious anemia, megacolon, and intestinal obstruction
- Bleeding tendencies
- Iron deficiency anemia
- Psychiatric disturbances
- Carpal tunnel syndrome
- Impaired fertility
- Benign intracranial hypertension
- Conductive or sensorineural deafness

Signs and symptoms

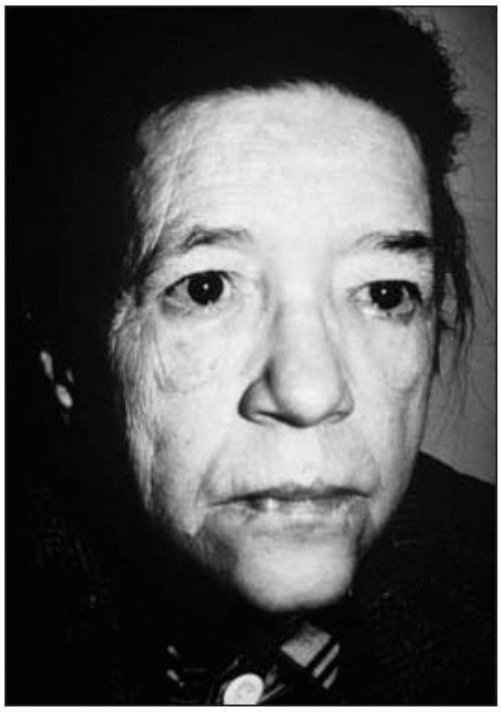
Typically, the early clinical features of hypothyroidism are vague: fatigue, menstrual changes, hypercholesterolemia, forgetfulness, sensitivity to cold, unexplained weight gain, and constipation. As the disorder progresses, characteristic myxedematous signs and symptoms

appear: decreasing mental stability; dry, flaky, inelastic skin; puffy face, hands, and feet; hoarseness; periorbital edema; upper eyelid droop; dry, sparse hair; and thick, brittle nails. (See *Facial signs of myxedema.*)

Cardiovascular involvement leads to decreased cardiac output, slow pulse rate, signs of poor peripheral circulation and, occasionally, an enlarged heart. Other common effects include anorexia, abdominal distention, menorrhagia, decreased libido, infertility, ataxia, intention tremor, and nystagmus. Reflexes show delayed relaxation time (especially in the Achilles tendon).

FACIAL SIGNS OF MYXEDEMA

Characteristic myxedematous signs in adults include dry, flaky, inelastic skin; puffy face; and upper eyelid droop.



ALERT

Progression to myxedema coma is usually gradual but when stress (such as hip fracture, infection, or myocardial infarction) aggravates severe or prolonged hypothyroidism, coma may develop abruptly. Clinical effects include progressive stupor, hypoventilation,

hypoglycemia, hyponatremia, hypotension, and hypothermia.

Diagnosis

CONFIRMING DIAGNOSIS

Radioimmunoassay confirms hypothyroidism with low triiodothyronine (T_3) and thyroxine (T_4) levels.

Supportive laboratory findings include:

- increased TSH level when hypothyroidism is due to thyroid insufficiency; decreased TSH level when hypothyroidism is due to hypothalamic or pituitary insufficiency
- elevated levels of serum cholesterol, alkaline phosphatase, and triglycerides
- normocytic normochromic anemia.

In myxedema coma, laboratory tests may also show low serum sodium levels, and decreased pH and increased partial pressure of carbon dioxide, indicating respiratory acidosis.

Treatment

Therapy for hypothyroidism consists of gradual thyroid replacement with levothyroxine (for low T_4 levels) and, occasionally, liothyronine (for inadequate T_3 levels).

During myxedema coma, effective treatment supports vital functions while restoring euthyroidism. To support blood pressure and pulse rate, treatment includes I.V. administration of levothyroxine and hydrocortisone to correct possible pituitary or adrenal insufficiency. Hypoventilation requires oxygenation and respiratory support. Other supportive measures include fluid replacement and antibiotics for infection.

Special considerations

To manage the hypothyroid patient:

- Provide a high-bulk, low-calorie diet and encourage activity to combat constipation and promote weight loss. Administer cathartics and stool softeners, as needed.
- After thyroid replacement therapy begins, watch for symptoms of hyperthyroidism, such as restlessness, sweating, and excessive weight loss.
- Tell the patient to report any signs of aggravated cardiovascular disease, such as chest pain and tachycardia.
- To prevent myxedema coma, tell the patient to continue his course of thyroid medication even if his symptoms subside.
- Warn the patient to report infection immediately and to make sure any physician who prescribes drugs for him knows about the underlying hypothyroidism.

Treatment of myxedema coma requires supportive care:

- Check frequently for signs of decreasing cardiac output such as falling urine output.
- Monitor temperature until stable. Provide extra blankets and clothing and a warm room to compensate for hypothermia. Rapid rewarming may cause vasodilation and vascular collapse.
- Record intake and output and daily weight. As treatment begins, urine output should increase and body weight decrease; if not, report this immediately.
- Turn the edematous bedridden patient every 2 hours, and provide skin care, particularly around bony prominences.
- Avoid sedation when possible or reduce dosage because hypothyroidism delays metabolism of many drugs.
- Maintain a patent I.V. line. Monitor serum electrolyte levels carefully when administering I.V. fluids.

ALERT

Monitor vital signs carefully when administering levothyroxine because rapid correction of hypothyroidism

can cause adverse cardiac effects. Report chest pain or tachycardia immediately. Watch for hypertension and heart failure in the elderly patient.

- Check arterial blood gas values for hypercapnia and hypoxia to determine whether the patient who's severely myxedematous requires ventilatory assistance.
- Because myxedema coma may have been precipitated by an infection, check possible sources of infection, such as blood or urine, and obtain sputum cultures.

Hypothyroidism in children

Deficiency of thyroid hormone secretion during fetal development or early infancy results in infantile cretinism (congenital hypothyroidism). Untreated hypothyroidism is characterized in infants by respiratory difficulties, persistent jaundice, and hoarse crying; in older children, by stunted growth (dwarfism), bone and muscle dystrophy, and mental deficiency.

Cretinism is three times more common in females than in males. Early diagnosis and treatment allow the best prognosis; infants treated before age 3 months usually grow and develop normally. However, athyroidic children who remain untreated beyond age 3 months and children with acquired hypothyroidism who remain untreated beyond age 2 suffer irreversible mental retardation; their skeletal abnormalities are reversible with treatment.

Causes and incidence

In infants, cretinism usually results from defective embryonic development that causes congenital absence or underdevelopment of the thyroid gland. The next most common cause can be traced to an inherited enzymatic defect in the synthesis of thyroxine (T_4) caused by an autosomal recessive gene. Less frequently, antithyroid drugs taken during pregnancy produce cretinism in infants. In children older than age 2, cretinism usually results from chronic autoimmune thyroiditis.

Complications

- Severe mental retardation
- Skeletal malformations (dwarfism, epiphyseal degeneration, and bone and muscle dystrophy)

Signs and symptoms

The weight and length of an infant with infantile cretinism appear normal at birth, but characteristic signs of hypothyroidism develop by the time he's 3 to 6 months old. In a breast-fed infant the onset of most symptoms may be delayed until weaning because breast milk contains small amounts of thyroid hormone.

Typically, an infant with cretinism sleeps excessively, seldom cries (except for occasional hoarse crying), and is inactive. Because of this, his parents may describe him as a “good baby—no trouble at all.” However, such behavior actually results from lowered metabolism and progressive mental impairment. The infant with cretinism also exhibits abnormal deep tendon reflexes, hypotonic abdominal muscles, a protruding abdomen, and slow, awkward movements. He has feeding difficulties, develops constipation and, because his immature liver can't conjugate bilirubin, becomes jaundiced.

His large, protruding tongue obstructs respiration, making breathing loud and noisy and forcing him to open his mouth to breathe. He may have dyspnea on exertion, anemia, abnormal facial features— such as a short forehead; puffy, wide-set eyes (periorbital edema); wrinkled eyelids; and a broad, short, upturned nose—and a dull expression, resulting from mental retardation. His skin is cold and mottled because of poor circulation, and his hair is dry, brittle, and dull. Teeth erupt late and tend to decay early; body temperature is below normal; and pulse rate is slow.

In the child who acquires hypothyroidism after age 2, appropriate treatment can prevent mental retardation. However, growth retardation becomes apparent in short stature (due to delayed epiphyseal maturation, particularly in the legs), obesity, and a head that appears

abnormally large because the arms and legs are stunted. An older child may show delayed or accelerated sexual development.

Diagnosis

A high serum level of thyroid-stimulating hormone (TSH), associated with low triiodothyronine and T_4 levels, points to cretinism. Because early detection and treatment can minimize the effects of cretinism, many states require measurement of infant thyroid hormone levels at birth.

Thyroid scan and radioactive iodine uptake tests show decreased uptake levels and confirm the absence of thyroid tissue in athyroidic children. Increased gonadotropin levels are compatible with sexual precocity in older children and may coexist with hypothyroidism.

Electrocardiogram shows bradycardia and flat or inverted T waves in untreated infants. Hip, knee, and thigh X-rays reveal absence of the femoral or tibial epiphyseal line and delayed skeletal development that's markedly inappropriate for the child's chronological age. A low T_4 level associated with a normal TSH level suggests hypothyroidism secondary to hypothalamic or pituitary disease, a rare condition.

Treatment

Early detection is mandatory to prevent irreversible mental retardation and permit normal physical development. Treatment of infants younger than age 1 consists of replacement therapy with oral levothyroxine, beginning with moderate doses. Dosage gradually increases to levels sufficient for lifelong maintenance. (Rapid increase in dosage may precipitate thyrotoxicity.) Doses are proportionately higher in children than in adults because children metabolize thyroid hormone more quickly.

Therapy in older children includes levothyroxine.

Special considerations

Prevention, early detection, comprehensive parent teaching, and psychological support are essential. Know the early signs. Be especially

wary if parents emphasize how good and how quiet their new baby is.

- During early management of infantile cretinism, monitor blood pressure and pulse rate; report hypertension and tachycardia immediately. But remember—normal infant heart rate is approximately 120 beats per minute. If the infant's tongue is unusually large, position him on his side and observe him frequently to prevent airway obstruction. Check rectal temperature every 2 to 4 hours. Keep the infant warm and his skin moist.
- Inform parents that the child will require lifelong treatment with thyroid supplements. Teach them to recognize signs of overdose: rapid pulse rate, irritability, insomnia, fever, sweating, and weight loss. Stress the need to comply with the treatment regimen to prevent further mental impairment.
- Provide support to help parents deal with a child who may be mentally retarded. Help them adopt a positive but realistic attitude and focus on their child's strengths rather than his weaknesses. Encourage them to provide stimulating activities to help the child reach his maximum potential. Refer them to the appropriate community resources for support.

PREVENTION

To prevent infantile cretinism, emphasize the importance of adequate nutrition during pregnancy, including iodine-rich foods and the use of iodized salt or, in case of sodium restriction, an iodine supplement.

Thyroiditis

Inflammation of the thyroid gland occurs as autoimmune thyroiditis (long-term inflammatory disease), subacute granulomatous thyroiditis (self-limiting inflammation), Riedel's thyroiditis (rare, invasive fibrotic process), and miscellaneous thyroiditis (acute suppurative, chronic infective, and chronic noninfective).

Causes and incidence

Autoimmune thyroiditis is due to antibodies to thyroid antigens in the blood. It may cause inflammation and lymphocytic infiltration (Hashimoto's thyroiditis). Glandular atrophy (myxedema) and Graves' disease are linked to autoimmune thyroiditis.

Subacute granulomatous thyroiditis usually follows mumps, influenza, coxsackievirus, or adenovirus infection. Riedel's thyroiditis is a rare condition of unknown etiology.

Miscellaneous thyroiditis results from bacterial invasion of the gland in acute suppurative thyroiditis; tuberculosis, syphilis, actinomycosis, or other infectious agents in the chronic infective form; and sarcoidosis and amyloidosis in chronic noninfective thyroiditis. Postpartum thyroiditis (silent thyroiditis) is another autoimmune disorder associated with transient thyroiditis in females within 1 year after delivery.

Thyroiditis is most prevalent among people ages 30 to 50 and is more common in women than in men. Incidence is highest in the Appalachian region of the United States.

Complications

- *Hasmimoto's*—compression of surrounding tissues
- *Subacute*—permanent hypothyroid or hyperthyroid condition
- *Pyrogenic*—rupture of abscess into mediastinum, trachea, or esophagus
- *Riedel's*—hypothyroidism, tracheal or esophageal compression, and necrosis or hemorrhage of compressed tissue

Signs and symptoms

Autoimmune thyroiditis is usually asymptomatic and commonly occurs in females, with peak incidence in middle age. It's the most prevalent cause of spontaneous hypothyroidism.

In subacute granulomatous thyroiditis, moderate thyroid enlargement may follow an upper respiratory tract infection or a sore throat. The thyroid may be painful and tender, and dysphagia may occur.

In Riedel's thyroiditis, the gland enlarges slowly as it's replaced by hard, fibrous tissues. This fibrosis may compress the trachea or the esophagus. The thyroid feels firm.

Clinical effects of miscellaneous thyroiditis are characteristic of pyogenic infection: fever, pain, tenderness, and reddened skin over the gland.

Diagnosis

Precise diagnosis depends on the type of thyroiditis:

- *Autoimmune:* high titers of thyroglobulin and microsomal antibodies present in serum
- *Subacute granulomatous:* elevated erythrocyte sedimentation rate, increased thyroid hormone levels, decreased thyroidal radioiodine uptake
- *Chronic infective and noninfective:* varied findings, depending on underlying infection or other disease.

Treatment

Appropriate treatment varies with the type of thyroiditis. Drug therapy includes levothyroxine for accompanying hypothyroidism, analgesics and anti-inflammatory drugs for mild subacute granulomatous thyroiditis, propranolol for transient hyperthyroidism, and steroids for severe episodes of acute inflammation. Suppurative thyroiditis requires antibiotic therapy. A partial thyroidectomy may be necessary to relieve tracheal or esophageal compression in Riedel's thyroiditis.

Special considerations

Before treatment, obtain a patient history to identify underlying diseases that may cause thyroiditis, such as tuberculosis or a recent viral infection.

- Check the patient's vital signs, and examine her neck for unusual swelling, enlargement, or redness. Provide a liquid diet if she has difficulty swallowing, especially when due to fibrosis. If the neck is

swollen, measure and record the circumference daily to monitor progressive enlargement.

- Administer antibiotics as indicated, and report and record elevations in temperature.
- Instruct the patient to watch for and report signs of hypothyroidism (lethargy, restlessness, sensitivity to cold, forgetfulness, and dry skin), especially if she has Hashimoto's thyroiditis, which often causes hypothyroidism.
- Check for signs of hyperthyroidism (nervousness, tachycardia, tremor, and weakness), which commonly occurs in subacute thyroiditis.
- After thyroidectomy, check vital signs every 15 to 30 minutes until the patient's condition stabilizes. Stay alert for signs of tetany secondary to accidental parathyroid injury during surgery. Keep 10% calcium gluconate available for I.V. use if needed. Assess dressings frequently for excessive bleeding. Watch for signs of airway obstruction, such as difficulty in talking or increased swallowing; keep tracheotomy equipment handy.
- Explain to the patient that she'll need lifelong thyroid hormone replacement therapy if hypothyroidism occurs. Tell her to watch for signs of overdosage, such as nervousness and palpitations.

Simple goiter

Simple (or nontoxic) goiter is a thyroid gland enlargement that isn't caused by inflammation or a neoplasm, and is commonly classified as endemic or sporadic. Endemic goiter usually results from inadequate dietary intake of iodine associated with such factors as iodine-depleted soil or malnutrition. Sporadic goiter follows ingestion of certain drugs or foods.

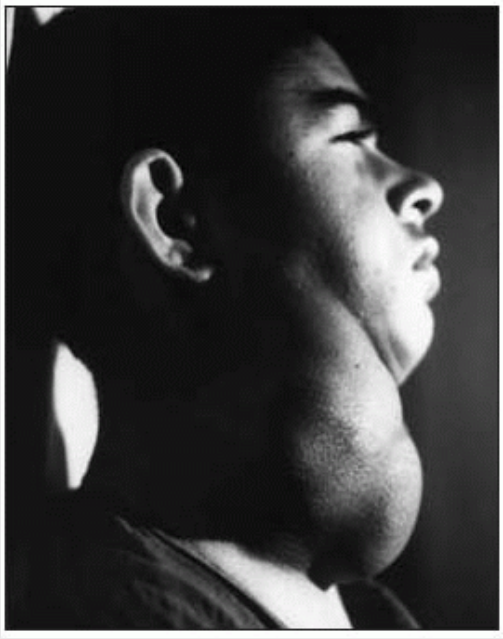
Simple goiter affects more females than males, especially during adolescence, pregnancy, and menopause, when the body's demand for thyroid hormone increases. Sporadic goiter affects no particular population segment. With appropriate treatment, the prognosis is good for either type of goiter.

Causes and incidence

Simple goiter occurs when the thyroid gland can't secrete enough thyroid hormone to meet metabolic requirements. As a result, the thyroid gland enlarges to compensate for inadequate hormone synthesis, a compensation that usually overcomes mild to moderate hormonal impairment. Because thyroid-stimulating hormone (TSH) levels are generally within normal limits in patients with simple goiter, goitrogenicity probably results from impaired intrathyroidal hormone synthesis and depletion of glandular iodine, which increases the thyroid gland's sensitivity to TSH. However, increased levels of TSH may be transient and therefore missed.

MASSIVE GOITER

Massive multinodular goiter causes gross distention and swelling of the neck.



Endemic goiter usually results from inadequate dietary intake of iodine, which leads to inadequate secretion of thyroid hormone. Since the introduction of iodized salt in the United States, cases of endemic goiter have virtually disappeared.

Sporadic goiter commonly results from the ingestion of large amounts of goitrogenic foods or the use of goitrogenic drugs. Goitrogenic foods,

such as rutabagas, cabbage, soybeans, peanuts, peaches, peas, strawberries, spinach, and radishes, contain agents that decrease thyroxine (T_4) production. Goitrogenic drugs include propylthiouracil, iodides, phenylbutazone, paraaminosalicylic acid, cobalt, and lithium. In a pregnant woman, these substances may cross the placenta and affect the fetus.

Inherited defects may be responsible for insufficient T_4 synthesis or impaired iodine metabolism. Because families tend to congregate in a single geographic area, this familial factor may contribute to the incidence of both endemic and sporadic goiters.

Females are more commonly affected than males. Incidence increases after age 40.

Complications

- Dysphagia
- Respiratory distress

Signs and symptoms

Thyroid enlargement may range from a mildly enlarged gland to a massive, multinodular goiter. (See *Massive goiter.*) Because simple goiter doesn't alter the patient's metabolic state, clinical features arise solely from enlargement of the thyroid gland. The patient may complain of respiratory distress and dysphagia from compression of the trachea and esophagus, and swelling and distention of the neck. In addition, large goiters may obstruct venous return, produce venous engorgement and, in rare cases, induce development of collateral venous circulation in the chest. Obstruction may cause dizziness or syncope (Pemberton's sign) when the patient raises her arms above her head.

Diagnosis

Diagnosis of simple goiter requires a thorough patient history and physical examination to rule out disorders with similar clinical effects, such as Graves' disease, Hashimoto's thyroiditis, and thyroid carcinoma. A detailed patient history may also reveal goitrogenic medications or

foods or endemic influence. The results of diagnostic laboratory tests include the following.

- TSH: high or normal levels
- Serum T_4 concentrations: low normal or normal
- Thyroid scan and uptake: normal or increased (50% of the dose at 24 hours)
- Ultrasound of thyroid: nodules may be present, necessitating biopsy for further evaluation.

Treatment

The goal of treatment is to reduce thyroid hyperplasia. Exogenous thyroid hormone replacement with levothyroxine is the treatment of choice; it inhibits TSH secretion and allows the gland to rest. Small doses of iodide (Lugol's or potassium iodide solution) commonly relieve goiter that's due to iodine deficiency. Sporadic goiter requires avoidance of known goitrogenic drugs and foods. A large goiter that's unresponsive to treatment may require subtotal thyroidectomy.

Special considerations

Patient care includes measuring the patient's neck circumference daily to check for progressive thyroid gland enlargement, and checking for the development of hard nodules in the gland, which may indicate carcinoma.

- To maintain constant hormone levels, instruct the patient to take the prescribed thyroid hormone preparations at the same time each day. Advise her to avoid taking the medicine at the same time as any calcium or iron-containing supplements (including prenatal vitamins), or with Metamucil, grapefruit, or grapefruit juice. Teach the patient and her family to identify and immediately report signs of thyrotoxicosis, including increased pulse rate, palpitations, diarrhea, sweating, tremors, agitation, and shortness of breath.
- Instruct the patient with endemic goiter to use iodized salt to supply the daily 150 to 300 mcg of iodine necessary to prevent goiter.

- Monitor the patient taking goitrogenic drugs for signs of sporadic goiter.

Hyperthyroidism

Hyperthyroidism (also known as *Graves disease*, *Basedow's disease*, or *thyrotoxicosis*) is a metabolic imbalance that results from thyroid hormone overproduction. The most common form of hyperthyroidism is Graves disease, which increases thyroxine (T_4) production, enlarges the thyroid gland (goiter), and causes multiple system changes.

With treatment, most patients can lead normal lives. However, *thyroid storm*—an acute exacerbation of hyperthyroidis— is an emergency that may lead to life-threatening cardiac, hepatic, or renal failure.

Causes and incidence

Hyperthyroidism may result from both genetic and immunologic factors. An increased incidence of this disorder in monozygotic twins, for example, points to an inherited factor, probably an autosomal recessive gene. This disease occasionally co-exists with abnormal iodine metabolism and other endocrine abnormalities, such as diabetes mellitus, hyperparathyroidism, and thyroiditis. Hyperthyroidism is also associated with autoantibody production (thyroid-stimulating immunoglobulin and thyroid-stimulating hormone [TSH]binding inhibitory immunoglobulin), possibly due to a defect in suppressor-T-lymphocyte function that allows the formation of autoantibodies.

In latent hyperthyroidism, excessive dietary intake of iodine and, possibly, stress can precipitate clinical hyperthyroidism. In a person with inadequately treated hyperthyroidism, stress—including surgery, infection, toxemia of pregnancy, and diabetic ketoacidosis—can precipitate thyroid storm. (See *Other forms of hyperthyroidism*, page 620.)

Incidence of Graves disease is highest between ages 30 and 40, especially in people with family histories of thyroid abnormalities; only 5% of hyperthyroid patients are younger than age 15.

Complications

- *Cardiovascular* (most common in elderly)—arrhythmias; especially atrial fibrillation, cardiac insuffiency, cardiac decompression, and resistance to usual dosages of cardiac glycosides
- Muscle weakness and atrophy
- Paralysis
- Osteoporosis
- Vitiligo and skin hyperpigmentation
- Corneal ulcers
- Myasthenia gravis
- Impaired fertility
- Decreased libido
- Gynecomastia

OTHER FORMS OF HYPERTHYROIDISM

- *Toxic adenoma*—a small, benign nodule in the thyroid gland that secretes thyroid hormone—is the second most common cause of hyperthyroidism. The cause of toxic adenoma is unknown; incidence is highest in the elderly. Clinical effects are essentially similar to those of Graves disease, except that toxic adenoma doesn't induce ophthalmopathy, pretibial myxedema, or acropachy. Presence of adenoma is confirmed by radioactive iodine (^{131}I) uptake and thyroid scan, which show a single hyperfunctioning nodule suppressing the rest of the gland. Treatment includes ^{131}I therapy, or surgery to remove adenoma after antithyroid drugs achieve a euthyroid state.
- *Thyrotoxicosis factitia* results from chronic ingestion of thyroid hormone for thyrotropin suppression in patients with thyroid carcinoma, or from thyroid hormone abuse by people who are trying to lose weight.

- *Functioning metastatic thyroid carcinoma* is a rare disease that causes excess production of thyroid hormone.
- *Thyroid-stimulating hormonesecreting pituitary tumor* causes overproduction of thyroid hormone.
- *Subacute thyroiditis* is a virusinduced granulomatous inflammation of the thyroid, producing transient hyperthyroidism associated with fever, pain, pharyngitis, and tenderness in the thyroid gland.
- *Silent thyroiditis* is a self-limiting, transient form of hyperthyroidism, with histologic thyroiditis but no inflammatory symptoms.

Signs and symptoms

The classic features of hyperthyroidism are an enlarged thyroid (goiter), nervousness, heat intolerance, weight loss despite increased appetite, sweating, diarrhea, tremor, and palpitations. Exophthalmos is considered most characteristic but is absent in many patients with hyperthyroidism. Many other symptoms are common because hyperthyroidism profoundly affects virtually every body system.

- *Central nervous system*—difficulty in concentrating because increased T_4 secretion accelerates cerebral function; excitability or nervousness due to increased basal metabolic rate; fine tremor, shaky handwriting, and clumsiness from increased activity in the spinal cord area that controls muscle tone; emotional instability and mood swings, ranging from occasional outbursts to overt psychosis
- *Skin, hair, and nails*—smooth, warm, flushed skin (patient sleeps with minimal covers and little clothing); fine, soft hair; premature graying and increased hair loss in both sexes; friable nails and onycholysis (distal nail separated from the bed); pretibial myxedema (dermopathy), producing thickened skin, accentuated hair follicles, raised red patches of skin that are itchy and sometimes painful, with occasional nodule formation (Microscopic examination shows increased mucin deposits.)

- *Cardiovascular system*—tachycardia; full, bounding pulse; wide pulse pressure; cardiomegaly; increased cardiac output and blood volume; visible point of maximal impulse; paroxysmal supraventricular tachycardia and atrial fibrillation (especially in the elderly); and occasionally, systolic murmur at the left sternal border
- *Respiratory system*—dyspnea on exertion and at rest, possibly from cardiac decompensation and increased cellular oxygen utilization
- *GI system*—possible anorexia; nausea and vomiting due to increased GI mobility and peristalsis; increased defecation; soft stools or, with severe disease, diarrhea; and liver enlargement
- *Musculoskeletal system*—weakness, fatigue, and muscle atrophy; rare coexistence with myasthenia gravis; generalized or localized paralysis associated with hypokalemia

  may occur; and occasional acropachy —soft-tissue swelling, accompanied by underlying bone changes where new bone formation occurs
- *Reproductive system*—in women, oligomenorrhea or amenorrhea, decreased fertility, higher incidence of spontaneous abortions; in men, gynecomastia due to increased estrogen levels; in both sexes, diminished libido
- *Eyes*—exophthalmos (from the combined effects of accumulation of mucopolysaccharides and fluids in the retroorbital tissues that force the eyeball outward, and of lid retraction that produces the characteristic staring gaze); occasional inflammation of conjunctivae, corneas, or eye muscles; diplopia; and increased tearing.

ALERT

When hyperthyroidism escalates to thyroid storm, these symptoms can be accompanied by extreme irritability, hypertension, tachycardia, vomiting, temperature up to 106° F (41.1° C), delirium, and coma.

Diagnosis

The diagnosis of hyperthyroidism is usually straightforward and depends on a careful clinical history and physical examination, a high index of suspicion, and routine hormone determinations.

CONFIRMING DIAGNOSIS

The following tests confirm the disorder:

- *Radioimmunoassay shows increased serum T_4 and triiodothyronine (T_3) concentrations.*
- *Thyroid scan reveals increased uptake of radioactive iodine (^{131}I). This test is contraindicated if the patient is pregnant.*
- *TSH levels are decreased.*
- *Ultrasonography confirms subclinical ophthalmopathy.*
- *Thyroid stimulating immunoglobulin is positive in Graves disease.*

Treatment

A number of approaches are used to treat hyperthyroidism, primarily antithyroid drugs, ^{131}I, and surgery. Appropriate treatment depends on the size of the goiter, the causes, the patient's age and parity, and how long surgery will be delayed (if the patient is an appropriate candidate for surgery).

Antithyroid drug therapy is used for children, young adults, pregnant females, and patients who refuse surgery or ^{131}I treatment. Thyroid hormone antagonists are given to block thyroid hormone synthesis. Although hypermetabolic symptoms subside within 4 to 8 weeks after such therapy begins, the patient must continue the medication for 6 months to 2 years, depending on the clinical circumstances. Beta-adrenergic blockers may be given concomitantly to manage tachycardia and other peripheral effects of excessive hypersympathetic activity.

During pregnancy, antithyroid medication should be kept at the minimum dosage required to keep maternal thyroid function within the high-normal range until delivery and to minimize the risk of fetal

hypothyroidism—even though most infants of hyperthyroid mothers are born with mild and transient hyperthyroidism.

PEDIATRIC TIP

Neonatal hyperthyroidism may even necessitate treatment with antithyroid medications and propranolol for 2 to 3 months.

Because hyperthyroidism is sometimes exacerbated in the puerperal period, continuous control of maternal thyroid function is essential. About 3 to 6 months postpartum, antithyroid drug administration can be gradually tapered and thyroid function reassessed. The mother receiving low-dose antithyroid treatment may breast-feed as long as the infant's thyroid function is checked periodically. Small amounts of the drug can be found in breast milk.

A single oral dose of ^{131}I is the treatment of choice for patients not planning to have children. (Patients of reproductive age must not be pregnant and should give informed consent for this treatment because small amounts of ^{131}I concentrate in the gonads. However, there have been no reports of damage to subsequently conceived children in more than 50 years of ^{131}I use.) During treatment with ^{131}I, the thyroid gland picks up the radioactive element as it would regular iodine. Subsequently, the radioactivity destroys some of the cells that normally concentrate iodine and produce T_4, thus decreasing thyroid hormone production

and normalizing thyroid size and function. In most patients, hypermetabolic symptoms diminish from 6 to 8 weeks after such treatment. However, some patients may require a second dose.

Subtotal (partial) thyroidectomy, which decreases the thyroid gland's capacity for hormone production, is indicated for patients with a large goiter whose hyperthyroidism has repeatedly relapsed after drug therapy or patients who refuse or aren't candidates for ^{131}I treatment. Preoperatively, the patient may receive iodides (Lugol's solution or saturated solution of potassium iodide), antithyroid drugs, or high doses of propranolol, to help prevent thyroid storm. If euthyroidism isn't achieved, surgery should be delayed and propranolol administered to

decrease the systemic effects (cardiac arrhythmias) caused by hyperthyroidism. After ablative treatment with ^{131}I or surgery, patients require regular medical supervision for the rest of their lives because they usually develop hypothyroidism, sometimes as long as several years after treatment.

Therapy for hyperthyroid ophthalmopathy includes local applications of topical medications but may require high doses of corticosteroids. A patient with severe exophthalmos that causes pressure on the optic nerve may require external beam radiation therapy or surgical decompression to lessen pressure on the orbital contents.

Treatment of thyroid storm includes administration of an antithyroid drug, propranolol I.V. to block sympathetic effects, a corticosteroid to inhibit the conversion of T_4 to T_3 and to replace depleted cortisol levels, and an iodide to block the release of thyroid hormone. Supportive measures include administration of nutrients, vitamins, fluids, and sedatives.

Special considerations

Patients with hyperthyroidism require vigilant care to prevent acute exacerbations and complications.

- Record vital signs and weight.
- Monitor serum electrolyte levels, and check periodically for hyperglycemia and glycosuria.

ELDER TIP

Carefully monitor cardiac function if the patient is elderly or has coronary artery disease. If the heart rate is more than 100 beats/minute, check blood pressure and pulse rate often.

- Check level of consciousness and urine output.

ALERT

If the patient is pregnant, tell her to watch closely during the first trimester for signs of spontaneous abortion and

to report such signs immediately.

- Encourage bed rest, and keep the patient's room cool, quiet, and dark. The patient with dyspnea will be most comfortable sitting upright or in high Fowler's position.
- Remember, extreme nervousness may produce bizarre behavior. Reassure the patient and his family that such behavior will probably subside with treatment. Provide sedatives as necessary.
- To promote weight gain, provide a balanced diet, with six meals a day. If the patient has edema, suggest a low-sodium diet.
- If iodide is part of the treatment, mix it with milk, juice, or water to prevent GI distress, and administer it through a straw to prevent tooth discoloration.

ALERT

Watch for signs of thyroid storm, such as tachycardia, hyperkinesis, fever, vomiting, and hypertension.

- Check intake and output carefully to ensure adequate hydration and fluid balance.
- Closely monitor blood pressure, cardiac rate and rhythm, and temperature. If the patient has a high fever, reduce it with appropriate hypothermic measures. Maintain an I.V. line and give drugs, as ordered.
- If the patient has exophthalmos or other ophthalmopathy, suggest sunglasses or eye patches to protect his eyes from light. Moisten the conjunctivae often with isotonic eye drops. Warn the patient with severe lid retraction to avoid sudden physical movements that might cause the lid to slip behind the eyeball. He should avoid cigarette smoke.
- Avoid excessive palpation of the thyroid to avoid precipitating thyroid storm.

Thyroidectomy necessitates meticulous postoperative care to prevent complications:

- Watch for evidence of hemorrhage into the neck, such as a tight dressing with no blood on it. Change dressings and perform wound care, as ordered; check the *back* of the dressing for drainage. Keep the patient in semi-Fowler's position, and support his head and neck with sandbags to ease tension on the incision.
- Check for dysphagia or hoarseness from possible laryngeal nerve injury.
- Watch for signs of hypoparathyroidism (tetany, numbness), a complication that results from accidental removal of the parathyroid glands during surgery.
- Stress the importance of regular medical follow-up after discharge because hypothyroidism may develop from 2 to 4 weeks postoperatively.

ALERT

Check often for respiratory distress, and keep a tracheotomy tray at bedside.

Drug therapy and ^{131}I therapy require careful monitoring and comprehensive patient teaching:

- After ^{131}I therapy, tell the patient not to expectorate or cough freely because his saliva will be radioactive for 24 hours. Stress the need for repeated measurement of serum T_4 levels.
- If the patient is taking propylthiouracil and methimazole, monitor complete blood count periodically to detect leukopenia, thrombocytopenia, and agranulocytosis. Instruct him to take these medications with meals to minimize GI distress and to avoid over-the-counter cough preparations because many contain iodine.
- Tell him to report fever, enlarged cervical lymph nodes, sore throat, mouth sores, and other signs of blood dyscrasias and any rash or skin eruptions—signs of hypersensitivity.
- Watch the patient taking propranolol for signs of hypotension (dizziness, decreased urine output). Tell him to rise slowly after sitting or lying down to prevent orthostatic syncope.

- Instruct the patient receiving antithyroid drugs or ^{131}I therapy to report any symptoms of hypothyroidism.

PARATHYROID GLANDS

Hypoparathyroidism

Hypoparathyroidism is a deficiency of parathyroid hormone (PTH) caused by disease, injury (usually surgical), or congenital malfunction of the parathyroid glands. Because the parathyroid glands primarily regulate calcium balance, hypoparathyroidism causes hypocalcemia, producing neuromuscular symptoms ranging from paresthesia to tetany. The clinical effects of hypoparathyroidism are usually correctable with replacement therapy. However, some complications of this disorder, such as cataracts and basal ganglion calcifications, are irreversible.

Causes and incidence

Hypoparathyroidism may be acute or chronic and is classified as idiopathic or acquired. The acquired form may also be reversible. *Idiopathic hypoparathyroidism* may result from an autoimmune genetic disorder or the congenital absence of the parathyroid glands. *Acquired hypoparathyroidism* commonly results from accidental removal of or injury to one or more parathyroid glands during thyroidectomy or other neck surgery; rarely it results from massive thyroid irradiation. It may also result from ischemic infarction of the parathyroids during surgery or from hemochromatosis, sarcoidosis, amyloidosis, tuberculosis, neoplasms, or trauma. An *acquired, reversible hypoparathyroidism* may result from hypomagnesemia-induced impairment of hormone synthesis, from suppression of normal gland function due to hypercalcemia, or from delayed maturation of parathyroid function. (See *What happens in acute hypoparathyroidism*, page 624.)

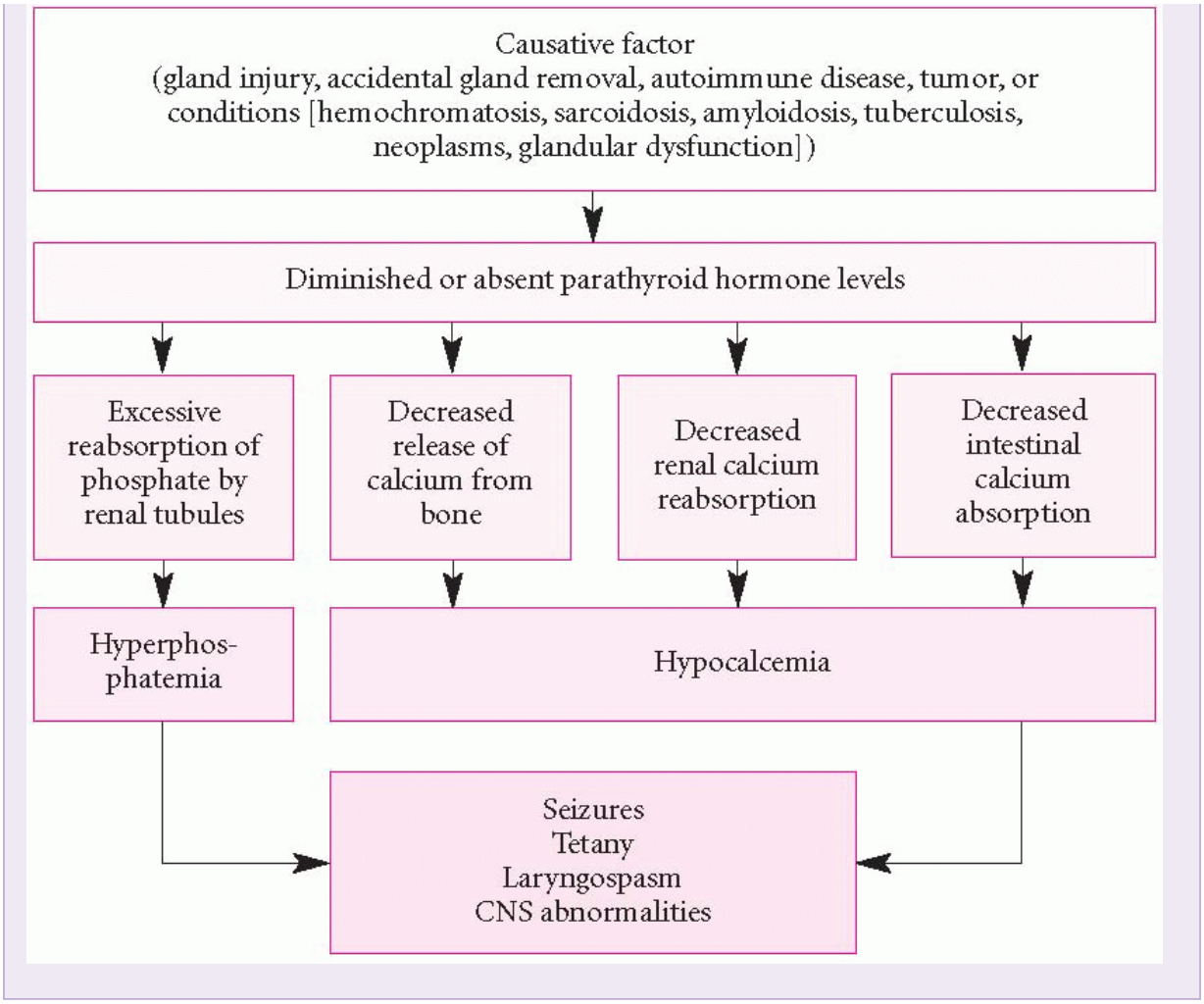
PTH isn't regulated by the pituitary or hypothalamus. It normally maintains blood calcium levels by increasing bone resorption and GI absorption of calcium. It also maintains an inverse relationship between serum calcium and phosphate levels by inhibiting phosphate reabsorption in

the renal tubules. Abnormal PTH production disrupts this balance. The incidence is 4 out of 100,000 people. Incidence of the idiopathic and reversible forms is highest in children; that of the irreversible acquired form, in older patients who have undergone surgery for hyperthyroidism or other head and neck conditions.

PATHOPHYSIOLOGY

WHAT HAPPENS IN ACUTE HYPOPARATHYROIDISM

Causes of acute hypoparathyroidism include injury to the glands, accidental removal of the parathyroid glands during thyroidectomy or other neck surgery, autoimmune disease, tumor, tuberculosis, sarcoidosis, hemochromatosis, and severe magnesium deficiency associated with alcoholism and intestinal malabsorption. These disorders and conditions cause a cascade of effects that result in severe hypocalcemia and hyperphosphatemia, which can lead to seizures, tetany, laryngospasm, and central nervous system (CNS) abnormalities, as shown in the flow chart below.



Complications

- Tetany
- Loss of consciousness
- Osteoporosis
- Slowed mental development in children
- Cataracts
- Arrhythmias

Signs and symptoms

Although mild hypoparathyroidism may be asymptomatic, it usually produces hypocalcemia and high serum phosphate levels that affect the

central nervous system (CNS) as well as other body systems. Chronic hypoparathyroidism typically causes neuromuscular irritability, increased deep tendon reflexes, Chvostek's sign (hyperirritability

of the facial nerve, producing a characteristic spasm when it's tapped), dysphagia, organic mental syndrome, psychosis, mental deficiency in children, and tetany.

Acute (overt) tetany begins with a tingling in the fingertips, around the mouth and, occasionally, in the feet. This tingling spreads and becomes more severe, producing muscle tension and spasms and consequent adduction of the thumbs, wrists, and elbows. Pain varies with the degree of muscle tension but seldom affects the face, legs, and feet. Chronic tetany is usually unilateral and less severe; it may cause difficulty in walking and a tendency to fall. Both forms of tetany can lead to laryngospasm, stridor and, eventually, cyanosis. They may also cause seizures. These CNS abnormalities tend to be exaggerated during hyperventilation, pregnancy, infection, withdrawal of thyroid hormone, therapy with loop diuretics, and before menstruation.

Other clinical effects include abdominal pain; dry, lusterless hair; spontaneous hair loss; brittle fingernails that develop ridges or fall out; dry, scaly skin; cataracts; and weakened tooth enamel, which causes teeth to stain, crack, and decay easily. Hypocalcemia may induce cardiac arrhythmias and may eventually lead to heart failure.

Diagnosis

CONFIRMING DIAGNOSIS

The following test results confirm the diagnosis of hypoparathyroidism:

- *Radioimmunoassay for PTH: decreased PTH concentration*
- *Serum calcium: decreased*
- *Serum phosphorus: increased*
- *Electrocardiogram (ECG): prolonged QT and ST intervals due to hypocalcemia.*

Inflating a blood pressure cuff on the upper arm to between diastolic and systolic blood pressure and maintaining this inflation for 3 minutes elicits Trousseau's sign (carpal spasm), thereby provoking clinical evidence of hypoparathyroidism.

Treatment

Because calcium absorption from the small intestine requires the presence of vitamin D, treatment includes vitamin D and calcium supplements. Therapy is usually lifelong, except for the reversible form of the disease. If the patient can't tolerate the pure form of vitamin D, alternatives include dihydrotachysterol, if hepatic and renal function is adequate, and calcitriol, if it's severely compromised. In patients with preexisting hypomagnesemia, this condition must be corrected to treat the resulting hypocalcemia. A high-calcium, lowphosphorous diet is recommended.

Acute life-threatening tetany requires immediate I.V. administration of calcium to raise serum calcium levels. The patient who's awake and able to cooperate can help raise serum calcium levels by breathing into a paper bag and then inhaling his own carbon dioxide; this produces hypoventilation and mild respiratory acidosis. Sedatives and anticonvulsants may control spasms until calcium levels rise. Chronic tetany requires maintenance therapy with oral calcium and vitamin D supplements.

Special considerations

ALERT

While awaiting diagnosis of hypoparathyroidism in a patient with a history of tetany, maintain a patent I.V. line and keep I.V. calcium available. Because the patient is vulnerable to seizures, maintain seizure precautions. Also, keep a tracheotomy tray and endotracheal tube at the bedside because laryngospasm may result from hypocalcemia.

- Instruct the patient to follow a high-calcium, low-phosphorus diet.

- When caring for the patient with chronic disease, particularly a child, stay alert for minor muscle twitching and for signs of laryngospasm because these effects may signal the onset of tetany.
- For the patient on drug therapy, emphasize the importance of checking serum calcium levels at least three times a year. Instruct the patient to watch for signs of hypercalcemia and to keep medications away from light and heat.
- Dental changes, cataracts, and brain calcifications are permanent. These can be prevented with early detection and periodic calcium determinations.

ALERT

Because the patient with chronic disease has prolonged QT intervals on ECG, watch for heart block and signs of decreasing cardiac output.

Because calcium potentiates the effect of cardiac glycosides, closely monitor the patient receiving both a cardiac glycoside and calcium. Stay alert for signs of digoxin toxicity, such as arrhythmias, nausea, fatigue, vision changes.

- Instruct the patient with scaly skin to use creams to soften his skin. Also, tell him to keep his nails trimmed to prevent them from splitting.
- Hyperventilation or recent blood transfusions may worsen tetany. (Anticoagulant in stored blood binds calcium.)
- For the patient with tetany, administer 10% calcium gluconate by slow I.V. infusion (1 ml/minute), and maintain a patent airway. The patient may also require intubation and sedation. Monitor vital signs often after administration sedation to make certain that blood pressure and heart rate return to normal.

Hyperparathyroidism

Hyperparathyroidism is characterized by overactivity of one or more of the four parathyroid glands, resulting in excessive secretion of parathyroid hormone (PTH). Hypersecretion of PTH promotes bone resorption and leads to hypercalcemia and hypophosphatemia, which in turn results in increased renal and GI absorption of calcium.

Causes and incidence

Hyperparathyroidism may be primary or secondary. In primary hyperparathyroidism, one or more of the parathyroid glands enlarges, increasing PTH secretion and elevating serum calcium levels. The most common cause is a single adenoma. Other causes include a genetic disorder or multiple endocrine neoplasia. Primary hyperparathyroidism usually occurs between ages 30 and 50 but can also occur in children and the elderly. It affects two to three times more females than males. It's a common disorder, affecting 1 in 1,000 people.

In secondary hyperparathyroidism, excessive compensatory production of PTH stems from a hypocalcemia-producing abnormality outside the parathyroid gland, which causes a resistance to the metabolic action of PTH. Some hypocalcemia-producing abnormalities are chronic renal failure, renal absorption disorders, vitamin D deficiency (especially in the housebound elderly), or osteomalacia due to phenytoin or laxative abuse.

Complications

- Osteoporosis
- Renal calculi
- Renal failure
- Hypertension
- Peptic ulcers
- Cardiac arrhythmias
- Heart failure

Signs and symptoms

Clinical effects of primary hyperparathyroidism result from hypercalcemia and are typically present in several body systems.

- *Renal system*—nephrocalcinosis due to elevated levels of calcium and, possibly, recurring nephrolithiasis, which may lead to renal insufficiency. Renal manifestations, including polyuria, are the most common effects of hyperparathyroidism.
- *Skeletal and articular system*—chronic low back pain and easy fracturing due to bone degeneration, bone tenderness, chondrocalcinosis, occasional severe osteopenia, especially on the vertebrae, erosions of the juxta-articular surface, subchondral fractures, traumatic synovitis, and pseudogout
- *GI system*—pancreatitis, causing constant, severe epigastric pain radiating to the back; peptic ulcers, causing abdominal pain, anorexia, nausea, and vomiting
- *Neuromuscular system*—marked muscle weakness and atrophy, particularly in the legs
- *Central nervous system*—psychomotor and personality disturbances, depression, overt psychosis, stupor and, possibly, coma
- *Other*—skin necrosis, cataracts, calcium microthrombi to lungs and pancreas, polyuria, anemia, and subcutaneous calcification.

Similarly, in secondary hyperparathyroidism, decreased serum calcium levels may produce the same features of calcium imbalance, with skeletal deformities of the long bones (rickets, for example) as well as symptoms of the underlying disease.

Diagnosis

CONFIRMING DIAGNOSIS

In primary disease, a high concentration of serum PTH on radioimmunoassay with accompanying hypercalcemia and hypercaluria confirms the diagnosis.

Laboratory tests reveal elevated calcium, chloride, and alkaline phosphatase levels and a decreased phosphatase level.

Hyperparathyroidism may also raise uric acid and creatinine levels and increase basal acid secretion and serum immunoreactive gastrin. Increased serum amylase levels may indicate acute pancreatitis.

Laboratory findings in secondary hyperparathyroidism show normal or slightly decreased serum calcium levels and variable serum phosphorus levels. Phosphorus can be quite elevated, especially in osteomalacia or renal disease. Patient history may reveal familial renal disease, seizure disorders, or drug ingestion. Other laboratory values and physical examination findings identify the cause of secondary hyperparathyroidism.

Treatment

Treatment varies, depending on the cause of the disease. Treatment of primary hyperparathyroidism may include surgery to remove the adenoma or, depending on the extent of hyperplasia, all but half of one gland (the remaining part of the gland is necessary to maintain normal PTH levels). Surgery may relieve bone pain within 3 days. However, renal damage may be irreversible.

Preoperatively—or if surgery isn't feasible or necessary—other treatments can decrease calcium levels. These include forcing fluids; limiting dietary intake of calcium; promoting sodium and calcium excretion through forced diuresis using normal saline solution (up to 6 L in life-threatening circumstances), furosemide, or ethacrynic acid; and administering oral sodium or potassium phosphate, subcutaneous calcitonin, I.V. plicamycin, or I.V. biphosphonates.

Therapy for potential postoperative magnesium and phosphate deficiencies includes I.V. administration of magnesium and phosphate, or sodium phosphate solution given orally or by retention enema. In addition, during the first 4 to 5 days after surgery, when serum calcium falls to low normal levels, supplemental calcium may be necessary; vitamin D or calcitriol may also be used to raise serum calcium levels.

Treatment of secondary hyperparathyroidism must correct the underlying cause of parathyroid hypertrophy. Vitamin D therapy or, in the patient with renal disease, administration of an oral calcium preparation (calcium acetate, if possible) for hyperphosphatemia, are typically used, although surgical excision may be necessary. In the

patient with renal failure, dialysis is necessary to lower calcium levels and may have to continue for the remainder of the patient's life. In the patient with chronic secondary hyperparathyroidism, the enlarged glands may not revert to normal size and function even after calcium levels have been controlled.

Special considerations

Care emphasizes prevention of complications from the underlying disease and its treatment.

- Obtain pretreatment baseline serum potassium, calcium, phosphate, and magnesium levels because these values may change abruptly during treatment.
- During hydration to reduce serum calcium level, record intake and output accurately. Strain urine to check for calculi. Provide at least 3 qt (3 L) of fluid a day, including cranberry or prune juice to increase urine acidity and help prevent calculus formation. As ordered, obtain blood and urine samples to measure sodium, potassium, and magnesium levels, especially for the patient taking furosemide.
- Auscultate for breath sounds often. Listen for signs of pulmonary edema in the patient receiving large amounts of saline solution I.V., especially if he has pulmonary or cardiac disease. Monitor the patient on digitalis glycosides carefully because elevated calcium levels can rapidly produce toxic effects.
- Because the patient is predisposed to pathologic fractures, take safety precautions to minimize the risk of injury. Assist him with walking, keep the bed at its lowest position, and raise the side rails. Lift the immobilized patient carefully to minimize bone stress. Schedule care to allow the patient with muscle weakness as much rest as possible.
- Watch for signs of peptic ulcer and administer antacids, as appropriate.

After parathyroidectomy:

- Check frequently for respiratory distress, and keep a tracheotomy tray at the bedside. Watch for postoperative complications, such as laryngeal nerve damage or, rarely, hemorrhage. Monitor intake and output carefully.
- Check for swelling at the operative site. Place the patient in semi-Fowler's position, and support his head and neck with sandbags to decrease edema, which may cause pressure on the trachea.
- Watch for signs of mild tetany, such as complaints of tingling in the hands and around the mouth. These symptoms should subside quickly but may be prodromal signs of tetany, so keep calcium gluconate or calcium chloride I.V. available for emergency administration. Watch for increased neuromuscular irritability and other signs of severe tetany, and report them immediately. Ambulate the patient as soon as possible postoperatively, even though he may find this uncomfortable, because pressure on bones speeds up bone recalcification.
- Check laboratory results for low serum calcium and magnesium levels.
- Monitor mental status and watch for listlessness. In the patient with persistent hypercalcemia, check for muscle weakness and psychiatric symptoms.
- Before discharge, advise the patient of the possible adverse effects of drug therapy. Emphasize the need for periodic follow-up through laboratory blood tests. If hyperparathyroidism wasn't corrected surgically, warn the patient to avoid calciumcontaining antacids and thiazide diuretics.

PREVENTION

Secondary hyperparathyroidism may be prevented by adequate intake of calcium in the diet or by addition of calcium supplements.

ADRENAL GLANDS

Adrenal hypofunction

Primary adrenal hypofunction (also called *adrenal insufficiency* or *Addison's disease*) originates within the adrenal gland itself and is

characterized by decreased mineralocorticoid, glucocorticoid, and androgen secretion. Adrenal hypofunction can also occur secondary to a disorder outside the gland (such as pituitary tumor, with corticotropin deficiency), but aldosterone secretion frequently continues intact. A relatively uncommon disorder, adrenal hypofunction can occur at any age and in both sexes. Secondary adrenal hypofunction occurs when a patient abruptly stops taking long-term exogenous steroid therapy. With early diagnosis and adequate replacement therapy, the prognosis for adrenal hypofunction is good.

Adrenal crisis (addisonian crisis), a critical deficiency of mineralocorticoids and glucocorticoids, generally follows acute stress, sepsis, trauma, surgery, or omission of steroid therapy in patients who have chronic adrenal insufficiency. A medical emergency, adrenal crisis necessitates immediate, vigorous treatment.

Causes and incidence

Adrenal hypofunction occurs when more than 90% of both adrenal glands are destroyed, an occurrence that typically results from an autoimmune process in which circulating antibodies react specifically against the adrenal tissue. Other causes include tuberculosis (once the chief cause; now responsible for less than 10% of adult cases), bilateral adrenalectomy, hemorrhage into the adrenal gland, neoplasms, and infections (acquired immunodeficiency syndrome, histoplasmosis, and cytomegalovirus). Rarely, a familial tendency to autoimmune disease predisposes the patient to adrenal hypofunction and other endocrinopathies.

Secondary adrenal hypofunction that results in glucocorticoid deficiency can stem from hypopituitarism (causing decreased corticotropin secretion), abrupt withdrawal

of long-term corticosteroid therapy (long-term exogenous corticosteroid stimulation suppresses pituitary corticotropin secretion and results in adrenal gland atrophy), or removal of a nonendocrine, corticotropin-secreting tumor. Adrenal crisis follows when trauma, surgery, or other physiologic stress exhausts the body's stores of glucocorticoids in a person with adrenal hypofunction.

Adrenal hypofunction affects 1 in 16,000 neonates congenitally. In adults, it affects 8 in 100,000 people, and males and females are affected equally. There's no racial predilection.

Complication

- Adrenal crisis

Signs and symptoms

Adrenal hypofunction typically produces such effects as weakness, fatigue, weight loss, and various GI disturbances, such as nausea, vomiting, anorexia, and chronic diarrhea. When primary, the disorder usually causes a conspicuous bronze coloration of the skin. The patient appears to be deeply suntanned, especially in the creases of the hands and over the metacarpophalangeal joints, the elbows, and the knees. He may also exhibit a darkening of scars, areas of vitiligo (absence of pigmentation), and increased pigmentation of the mucous membranes, especially the gingival mucosa. Abnormal skin and mucous membrane coloration results from decreased secretion of cortisol (one of the glucocorticoids), which causes the pituitary gland to simultaneously secrete excessive amounts of corticotropin and melanocyte-stimulating hormone (MSH).

Associated cardiovascular abnormalities in adrenal hypofunction include orthostatic hypotension, decreased cardiac size and output, and a weak, irregular pulse. Other clinical effects include decreased tolerance for even minor stress, poor coordination, fasting hypoglycemia (due to decreased gluconeogenesis), and a craving for salty food. Adrenal hypofunction may also retard axillary and pubic hair growth in females, decrease the libido (from decreased androgen production) and, in severe cases, cause amenorrhea.

Secondary adrenal hypofunction produces similar clinical effects but without hyperpigmentation because corticotropin and MSH levels are low. Because aldosterone secretion may continue at fairly normal levels in secondary adrenal hypofunction, this condition doesn't necessarily cause accompanying hypotension and electrolyte abnormalities.

ALERT

Adrenal crisis produces profound weakness, fatigue, nausea, vomiting, hypotension, dehydration and, occasionally, high fever followed by hypothermia. If untreated, this condition can ultimately lead to vascular collapse, renal shutdown, coma, and death.

Diagnosis

Diagnosis requires demonstration of decreased corticosteroid concentrations in plasma and an accurate classification of adrenal hypofunction as primary or secondary. If secondary adrenal hypofunction is suspected, the metyrapone test is indicated. This test requires oral or I.V. administration of metyrapone, which blocks cortisol production and should stimulate the release of corticotropin from the hypothalamic-pituitary system. In adrenal hypofunction, the hypothalamic-pituitary system responds normally, and plasma reveals high levels of corticotropin; however, plasma levels of cortisol precursor and urinary concentrations of 17-hydroxycorticosteroids don't rise.

If either primary or secondary adrenal hypofunction is suspected, a short corticotropin stimulation test may be done. If both corticotropin and cortisol are low, the long corticotropin test may be done. The test involves I.V. administration of corticotropin over 6 to 8 hours, after samples have been obtained to determine baseline plasma cortisol and 24-hour urine cortisol levels. In adrenal hypofunction, plasma and urine cortisol levels fail to rise normally in response to corticotropin; in secondary hypofunction, repeated doses of corticotropin over successive days produce a gradual increase in cortisol levels until normal values are reached.

In a patient with typical addisonian symptoms, the following laboratory findings

strongly suggest acute adrenal hypofunction:

- decreased cortisol levels in plasma (less than 10 mcg/dl in the morning, with lower levels in the evening); however, this test is time-consuming, and emergency therapy shouldn't be postponed for test results

- decreased serum sodium and fasting blood glucose levels
- increased serum potassium and blood urea nitrogen levels
- elevated hematocrit and lymphocyte and eosinophil counts
- X-rays showing a small heart and adrenal calcification.

Treatment

For all patients with primary or secondary adrenal hypofunction, corticosteroid replacement, usually with cortisone or hydrocortisone (both of which also have a mineralocorticoid effect), is the primary treatment and must continue throughout life. Adrenal hypofunction may also necessitate treatment with I.V. desoxycorticosterone, a pure mineralocorticoid, or oral fludrocortisone, a synthetic mineralocorticoid; both prevent dangerous dehydration and hypotension.

Adrenal crisis requires prompt I.V. bolus administration of hydrocortisone. Later, doses are given I.M. or are diluted with dextrose in saline solution and given I.V. until the patient's condition stabilizes.

With proper treatment, adrenal crisis usually subsides quickly; the patient's blood pressure should stabilize, and water and sodium levels should return to normal. After the crisis, maintenance doses of hydrocortisone preserve physiologic stability.

Special considerations

In adrenal crisis, monitor vital signs carefully, especially for hypotension, volume depletion, and other signs of shock (decreased level of consciousness and urine output). Watch for hyperkalemia before treatment and for hypokalemia after treatment (from excessive mineralocorticoid effect).

- If the patient also has diabetes, check blood glucose levels periodically because steroid replacement may require adjustment of insulin dosage.
- Record weight and intake and output carefully because the patient may have volume depletion. Until onset of mineralocorticoid effect, force fluids to replace excessive fluid loss.

To manage the patient receiving maintenance therapy:

- Arrange for a diet that maintains sodium and potassium balances.
- If the patient is anorectic, suggest six small meals a day to increase calorie intake. Ask the dietitian to provide a diet high in protein and carbohydrates. Keep a latemorning snack available in case the patient becomes hypoglycemic.
- Observe the patient receiving steroids for cushingoid signs such as fluid retention around the eyes and face. Watch for fluid and electrolyte imbalance, especially if the patient is receiving mineralocorticoids. Monitor weight and check blood pressure to assess body fluid status. Remember, steroids administered in the late afternoon or evening may cause stimulation of the central nervous system and insomnia in some patients. Check for petechiae because the patient bruises easily.
- If the patient receives glucocorticoids alone, monitor him for orthostatic hypotension or electrolyte abnormalities, which may indicate a need for mineralocorticoid therapy.
- Explain that lifelong steroid therapy is necessary.
- Teach the patient the symptoms of too great or too little a dose.
- Tell the patient that dosage may need to be increased during times of stress (when he has a cold, for example).
- Warn that infection, injury, or profuse sweating in hot weather may precipitate adrenal crisis.
- Warn the patient that any stress may necessitate additional cortisone to prevent adrenal crisis.
- Instruct the patient to always carry a medical identification card stating that he takes a steroid and giving the name of the drug and the dosage.

- Tell the patient to keep an emergency kit available containing hydrocortisone in a prepared syringe for use in times of stress.
- Teach the patient how to give himself an injection of hydrocortisone.

Cushing's syndrome

Cushing's syndrome is a cluster of clinical abnormalities caused by excessive levels of adrenocortical hormones (particularly cortisol) or related corticosteroids and, to a lesser extent, androgens and aldosterone. Its unmistakable signs include rapidly developing adiposity of the face (moon face), neck, and trunk and purple striae on the skin. (See *Symptoms of cushingoid syndrome*, page 632.) The prognosis depends on the underlying cause; it's poor in untreated people and in those with untreatable ectopic corticotropin-producing carcinoma.

Causes and incidence

In approximately 70% of patients, Cushing's syndrome results from excessive production of corticotropin and consequent hyperplasia of the adrenal cortex. Overproduction of corticotropin may stem from pituitary hypersecretion (Cushing's disease), a corticotropin-producing tumor in another organ (particularly bronchogenic or pancreatic cancer), or excessive administration of exogenous glucocorticoids.

In the remaining 30% of patients, Cushing's syndrome results from a cortisolsecreting adrenal tumor, which is usually benign. In infants, the usual cause of Cushing's syndrome is adrenal carcinoma.

Cushing's syndrome affects 13 of every 1 million people. It's more common in women than in men and occurs primarily between ages 25 and 40.

Complications

- Osteoporosis
- Pathologic fractures
- Peptic ulcer
- Impaired glucose tolerance
- Frequent infections
- Slow wound healing
- Hypertension

- Ischemic heart disease
- Heart failure
- Menstrual disturbances
- Sexual dysfunction

Signs and symptoms

Like other endocrine disorders, Cushing's syndrome induces changes in multiple body systems, depending on the adrenocortical hormone involved. Clinical effects may include the following.

- *Endocrine and metabolic systems*—diabetes mellitus, with decreased glucose tolerance, fasting hyperglycemia, and glycosuria
- *Musculoskeletal system*—muscle weakness due to hypokalemia or to loss of muscle mass from increased catabolism, pathologic fractures due to decreased bone mineral, and skeletal growth retardation in children
- *Skin*—purplish striae; fat pads above the clavicles, over the upper back (buffalo hump), on the face (moon face), and throughout the trunk, with slender arms and legs; little or no scar formation; poor wound healing; acne and hirsutism in females
- *GI system*—peptic ulcer, resulting from increased gastric secretions and pepsin production, and decreased gastric mucus
- *Central nervous system (CNS)*—irritability and emotional lability, ranging from euphoric behavior to depression or psychosis; insomnia
- *Cardiovascular system*—hypertension due to sodium and water retention; left ventricular hypertrophy; capillary weakness due to protein loss, which leads to bleeding, petechiae, and ecchymosis
- *Immune system*—increased susceptibility to infection due to decreased lymphocyte production and suppressed antibody formation; decreased resistance to stress (Suppressed inflammatory response may mask even a severe infection.)
- *Renal and urologic systems*—sodium and secondary fluid retention, increased potassium excretion, inhibited antidiuretic hormone

secretion, ureteral calculi from increased bone demineralization with hypercalciuria

- *Reproductive system*—increased androgen production with clitoral hypertrophy,

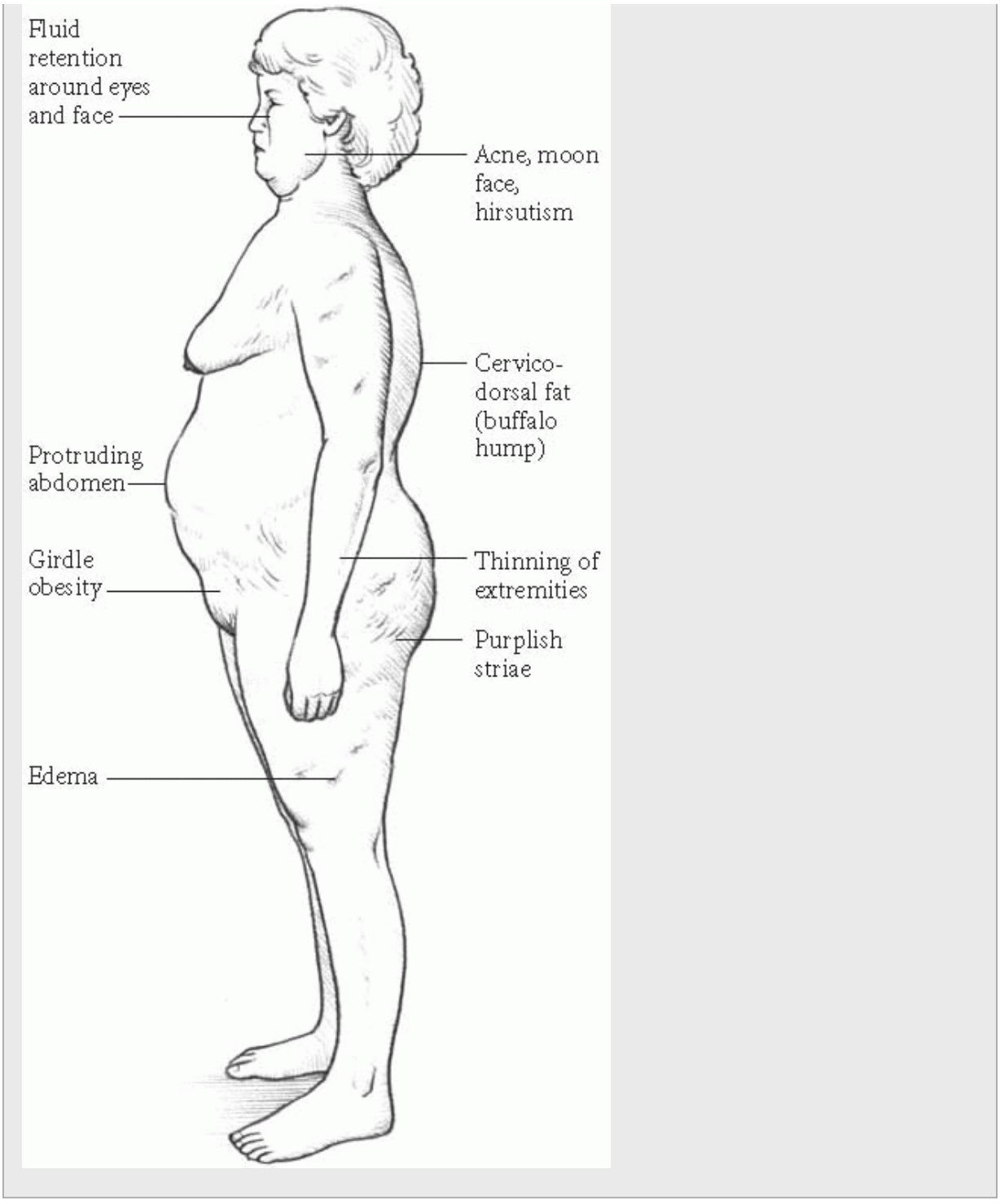
mild virilism, and amenorrhea or oligomenorrhea in women. Sexual dysfunction also occurs.

SYMPTOMS OF CUSHINGOID SYNDROME

Chronic depression, alcoholism, and long-term treatment with corticosteroids may produce an adverse effect called *cushingoid syndrome*—a condition marked by obvious fat deposits between the shoulders and around the waist, and widespread systemic abnormalities.

Differentiating between cushingoid syndrome and Cushing's syndrome can be difficult, so in addition to the symptoms shown in the illustration at right, observe for signs of hypertension, renal disorders, hyperglycemia, tissue wasting, muscle weakness, and labile emotional state. The patient may also have amenorrhea and glycosuria.

Resolution of the underlying disorder results in disappearance of cushingoid symptoms.



Diagnosis

Initially, diagnosis of Cushing's syndrome requires determination of plasma steroid levels. In people with normal hormone balance, plasma cortisol levels are higher in the morning and decrease gradually

throughout the day (diurnal variation). In patients with Cushing's syndrome, cortisol levels don't fluctuate and typically remain consistently elevated; 24-hour urine sample demonstrates elevated free cortisol levels.

CONFIRMING DIAGNOSIS

A low-dose dexamethasone suppression test confirms the diagnosis of Cushing's syndrome. Salivary cortisol levels collected at midnight (usually performed on an outpatient basis) are elevated and are the most sensitive confirmatory test. (See Diagnosing Cushing's syndrome, page 634.*)*

A high-dose dexamethasone suppression test can determine if Cushing's syndrome results from pituitary dysfunction (Cushing's disease). In this test, dexamethasone suppresses plasma cortisol levels, and urinary 17-hydroxycorticosteroid (17-OHCS) and 17-ketogenic steroid levels fall to 50% or less of basal levels. Failure to suppress these levels indicates that the syndrome results from an adrenal tumor or a nonendocrine, corticotropin-secreting tumor. This test can produce false-positive results.

In a stimulation test, administration of metyrapone, which blocks cortisol production by the adrenal glands, tests the ability of the pituitary gland and the hypothalamus to detect and correct low levels of plasma cortisol by increasing corticotropin production. The patient with Cushing's disease reacts to this stimulus by secreting an excess of plasma corticotropin as measured by levels of urinary 17-OHCS. If the patient has an adrenal or a nonendocrine corticotropin-secreting tumor, the pituitary gland—which is suppressed by the high cortisol levels—can't respond normally, so steroid levels remain stable or fall.

Ultrasound, computed tomography (CT) scan, or angiography localizes adrenal tumors; CT scan and magnetic resonance imaging of the head may identify pituitary tumors.

Treatment

Treatment to restore hormone balance and reverse Cushing's syndrome may necessitate radiation, drug therapy, or surgery. For example, pituitary-dependent Cushing's syndrome with adrenal hyperplasia and severe cushingoid symptoms (such as psychosis, poorly controlled diabetes mellitus, osteoporosis, and severe pathologic fractures) may require partial or complete hypophysectomy or pituitary irradiation. If the patient fails to respond, bilateral adrenalectomy may be performed. Nonendocrine corticotropin-producing tumors require excision of the tumor, followed by drug therapy (for example, with mitotane, metyrapone, or aminoglutethimide) to decrease cortisol levels if symptoms persist.

Aminoglutethimide and ketoconazole decrease cortisol levels and have been beneficial for many cushingoid patients. Aminoglutethimide alone, or in combination with metyrapone, may also be useful in metastatic adrenal carcinoma.

Before surgery, the patient with cushingoid symptoms should have special management to control hypertension, edema, diabetes, and cardiovascular manifestations and to prevent infection. Glucocorticoid administration on the morning of surgery can help prevent acute adrenal hypofunction during surgery.

Cortisol therapy is essential during and after surgery, to help the patient tolerate the physiologic stress imposed by removal of the pituitary or adrenals. If normal cortisol production resumes, steroid therapy may be gradually tapered and eventually discontinued. However, bilateral adrenalectomy or total hypophysectomy mandates lifelong steroid replacement therapy to correct hormonal deficiencies.

Special considerations

Patients with Cushing's syndrome require painstaking assessment and vigorous supportive care.

- Frequently monitor vital signs, especially blood pressure. Carefully observe the hypertensive patient who also has cardiac disease.
- Check laboratory reports for hypernatremia, hypokalemia, hyperglycemia, and glycosuria.

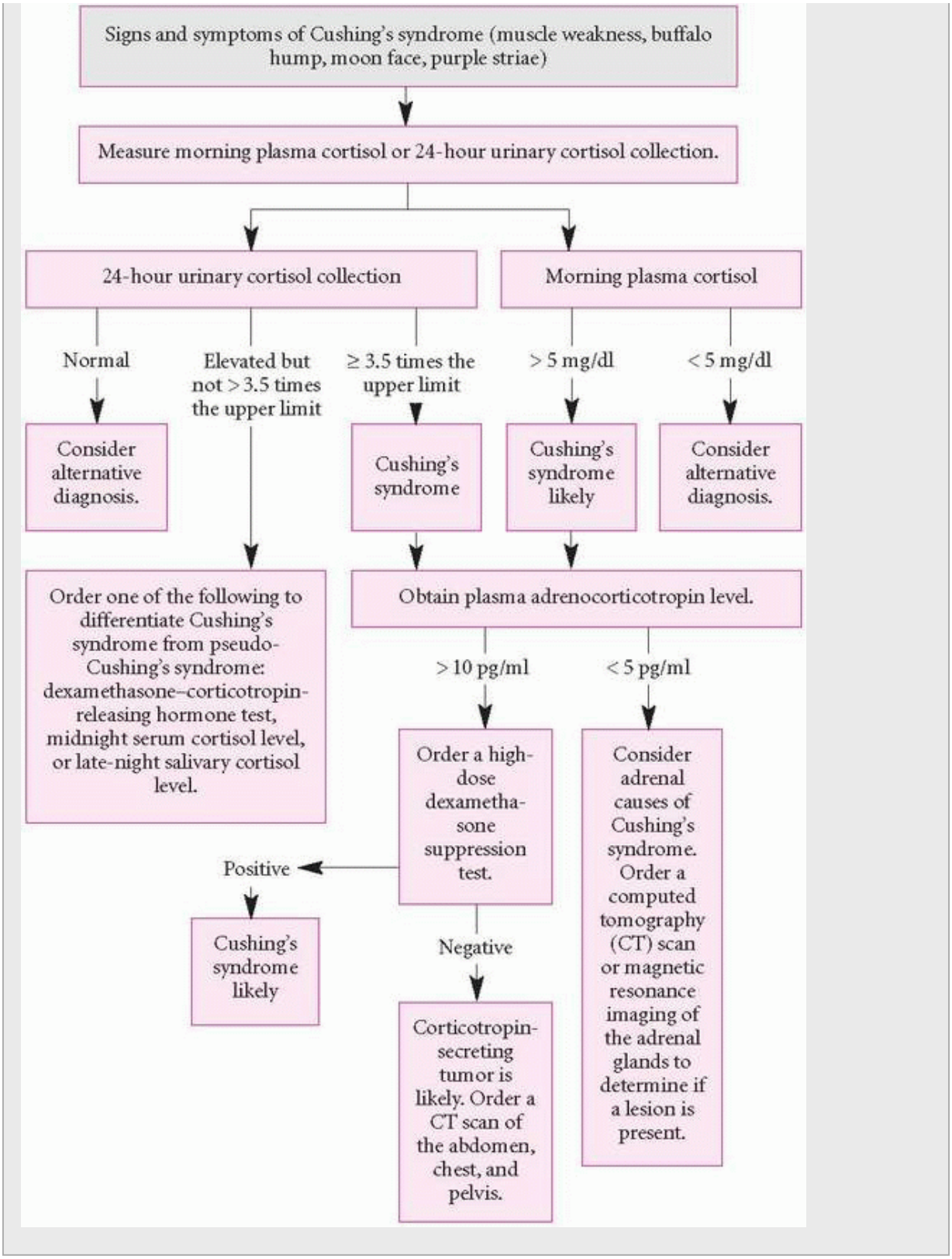
- Because the cushingoid patient is likely to retain sodium and water, check for edema, and monitor daily weight and intake and output carefully. To minimize weight gain, edema, and hypertension, ask the dietary department to provide a diet that's high in protein and potassium but low in calories, carbohydrates, and sodium.
- Watch for infection—a particular problem in Cushing's syndrome.
- If the patient has osteoporosis and is bedridden, perform passive range-of-motion exercises carefully because of the severe risk for pathologic fractures.
- Remember, Cushing's syndrome produces emotional lability. Record incidents that upset the patient, and try to prevent such situations from occurring if possible.

Help him get the physical and mental rest he needs—by sedation if necessary. Offer support to the emotionally labile patient throughout the difficult testing period.

DIFFERENTIAL DIAGNOSIS

DIAGNOSING CUSHING'S SYNDROME

The flowchart below aids in differential diagnosis of Cushing's syndrome.



After bilateral adrenalectomy and pituitary surgery:

- Report wound drainage or temperature elevation to the patient's physician immediately. Use strict sterile technique in changing the patient's dressings.
- Administer analgesics and replacement steroids, as ordered.
- Monitor urine output, and check vital signs carefully, watching for signs of shock (decreased blood pressure, increased pulse rate, pallor, and cold, clammy skin). To counteract shock, give vasopressors and increase the rate of I.V. fluids, as ordered. Because mitotane, aminoglutethimide, and metyrapone decrease mental alertness and produce physical weakness, assess neurologic and behavioral status, and warn the patient of adverse CNS effects. Also watch for severe nausea, vomiting, and diarrhea.
- Check laboratory reports for hypoglycemia due to removal of the source of cortisol, a hormone that maintains blood glucose levels.
- Check for abdominal distention and return of bowel sounds after adrenalectomy.
- Check regularly for signs of adrenal hypofunction—orthostatic hypotension, apathy, weakness, fatigue—indicators that steroid replacement is inadequate.
- In the patient undergoing pituitary surgery, check for and immediately report signs of increased intracranial pressure (confusion, agitation, changes in level of consciousness, nausea, hypotension, and vomiting). Watch for hypopituitarism.

Provide comprehensive teaching to help the patient cope with lifelong treatment:

- Advise the patient to take replacement steroids with antacids or meals, to minimize gastric irritation. (Usually it's helpful to take two-thirds of the dosage in the morning and the remaining third in the early afternoon to mimic diurnal adrenal secretion.)
- Tell the patient to carry a medical identification card and to immediately report physiologically stressful situations such as infections, which necessitate increased dosage.

- Instruct the patient to watch closely for signs of inadequate steroid dosage (fatigue, weakness, dizziness) and of overdosage (severe edema, weight gain). Emphatically warn against abrupt discontinuation of steroid dosage because this may produce a fatal adrenal crisis.
- Teach the patient about using IM hydrocortisone if he can't tolerate oral steroids.

Hyperaldosteronism

In hyperaldosteronism (Conn's syndrome), hypersecretion of the mineralocorticoid aldosterone by the adrenal cortex causes excessive reabsorption of sodium and water, and excessive renal excretion of potassium.

Causes and incidence

Hyperaldosteronism may be primary (uncommon) or secondary. In 70% of patients, hyperaldosteronism results from a benign aldosterone-producing adrenal adenoma. In 15% to 30% of patients, the cause is unknown; rarely, the cause is bilateral adrenocortical hyperplasia (in children) or carcinoma. Incidence is three times higher in females than in males and is highest between ages 30 and 50.

In primary hyperaldosteronism, chronic aldosterone excess is independent of the renin-angiotensin system and, in fact, suppresses plasma renin activity. This aldosterone excess enhances sodium reabsorption by the kidneys, which leads to mild hypernatremia and, simultaneously, hypokalemia and increased extracellular fluid (ECF) volume. Expansion of intravascular fluid volume also occurs and results in volumedependent hypertension and increased cardiac output. Excessive ingestion of English black licorice or licorice-like substances can produce a syndrome similar to primary hyperaldosteronism due to the mineralocorticoid action of glycyrrhizic acid.

Secondary hyperaldosteronism results from an extra-adrenal abnormality that stimulates the adrenal gland to increase production of aldosterone. For example, conditions that reduce renal blood flow (renal artery stenosis) and ECF volume or produce a sodium deficit activate the

renin-angiotensin system and, subsequently, increase aldosterone secretion. Thus, secondary hyperaldosteronism may result from conditions that induce hypertension through increased renin production (such as Wilms' tumor), ingestion of hormonal contraceptives, and pregnancy.

However, secondary hyperaldosteronism may also result from disorders unrelated to hypertension, which may or may not cause edema. For example, nephrotic syndrome, hepatic cirrhosis with ascites, and heart failure commonly induce edema, whereas Bartter's syndrome and salt-losing nephritis don't.

Complications

- Neuromuscular irritability
- Tetany
- Parasthesia
- Seizures
- Arrhythmias
- Ischemic heart disease
- Left ventricular hypertrophy
- Heart failure

Signs and symptoms

Most clinical effects of hyperaldosteronism result from hypokalemia, which increases neuromuscular irritability and produces muscle weakness; intermittent, flaccid paralysis; fatigue; headaches; paresthesia; and, possibly, tetany (resulting from metabolic alkalosis), which can lead to hypocalcemia.

Diabetes mellitus is common, perhaps because hypokalemia interferes with normal insulin secretion. Hypertension and its accompanying complications are also common. Other characteristic findings include visual disturbances and loss of renal concentrating ability, resulting in

nocturnal polyuria and polydipsia. Azotemia indicates chronic potassium depletion nephropathy.

Diagnosis

Persistently low serum potassium levels in a nonedematous patient who isn't taking diuretics, who doesn't have obvious GI losses (from vomiting or diarrhea), and who has a normal sodium intake, suggest hyperaldosteronism. If hypokalemia develops in a hypertensive patient shortly after starting treatment with potassium-wasting diuretics (such as thiazides), and if it persists after the diuretic has been discontinued and potassium replacement therapy has been instituted, evaluation for hyperaldosteronism is necessary.

CONFIRMING DIAGNOSIS

A low plasma renin level that fails to increase appropriately during volume depletion (upright posture, sodium depletion) and a high plasma aldosterone level during volume expansion by salt loading confirm primary hyperaldosteronism in a hypertensive patient without edema.

The serum bicarbonate level is often elevated, with ensuing alkalosis due to hydrogen and potassium ion loss in the distal renal tubules. Other tests show markedly increased urinary aldosterone levels, increased plasma aldosterone levels and, in secondary hyperaldosteronism, increased plasma renin levels.

A suppression test is useful to differentiate between primary and secondary hyperaldosteronism. During this test, the patient receives oral desoxycorticosterone for 3 days while plasma aldosterone levels and urinary metabolites are continuously measured. These levels decrease in secondary hyperaldosteronism but remain the same in primary hyperaldosteronism. Simultaneously, renin levels are low in primary hyperaldosteronism and high in secondary hyperaldosteronism.

Other helpful diagnostic evidence includes an increase in plasma volume of 30% to 50% above normal, electrocardiogram signs of hypokalemia (ST-segment depression and U waves), chest X-ray showing left ventricular

hypertrophy from chronic hypertension, and localization of the tumor by adrenal angiography or computed tomography scan.

Treatment

Although treatment of primary hyperaldosteronism may include unilateral adrenalectomy, administration of a potassium-sparing diuretic—spironolactone—and sodium restriction may control hyperaldosteronism without surgery. For bilateral adrenal hyperplasia, spironolactone is the drug of choice. Treatment of secondary hyperaldosteronism must include correction of the underlying cause.

Special considerations

Patient care includes careful monitoring and recording of urine output, blood pressure, weight, and serum potassium levels.

- Watch for signs of tetany (muscle twitching, Chvostek's sign) and for hypokalemia-induced cardiac arrhythmias, paresthesia, or weakness. Give potassium replacement, as ordered, and keep calcium gluconate I.V. available.
- Ask the dietitian to provide a low-sodium, high-potassium diet.
- After adrenalectomy, watch for weakness, hyponatremia, rising serum potassium levels, and signs of adrenal hypofunction, especially hypotension.
- If the patient is taking spironolactone, advise him to watch for signs of hyperkalemia. Tell him that impotence and gynecomastia may follow long-term use.
- Tell the patient who must take steroid hormone replacement to wear a medical identification bracelet.

Adrenogenital syndrome

Adrenogenital syndrome results from disorders of adrenocortical steroid biosynthesis. This syndrome may be inherited (congenital adrenal hyperplasia [CAH]) or acquired, usually as a result of an adrenal tumor

(adrenal virilism). Salt-losing CAH may cause fatal adrenal crisis in neonates.

Causes and incidence

CAH is transmitted as an autosomal recessive trait that causes deficiencies in the enzymes needed for adrenocortical secretion of cortisol and, possibly, aldosterone. Compensatory secretion of corticotropin produces varying degrees of adrenal hyperplasia. In simple virilizing CAH, deficiency of the enzyme 21-hydroxylase results in underproduction of cortisol. In turn, this cortisol deficiency stimulates increased secretion of corticotropin, producing large amounts of cortisol precursors and androgens that don't require 21-hydroxylase for synthesis.

In salt-losing CAH, 21-hydroxylase is almost completely absent. Corticotropin secretion increases, causing excessive production of cortisol precursors, including salt-wasting compounds. However, plasma cortisol and aldosterone levels—both dependent on 21-hydroxylase—fall precipitously and, in combination with the excessive production of salt-wasting compounds, precipitate acute adrenal crisis. Corticotropin hypersecretion stimulates adrenal androgens, possibly even more than in simple virilizing CAH, and produces masculinization. Other rare CAH enzyme deficiencies exist and lead to increased or decreased production of affected hormones.

CAH is the most prevalent adrenal disorder in infants and children; simple virilizing CAH and salt-losing CAH are the most common forms. Acquired adrenal virilism is rare and affects twice as many females as males. About 1 in 10,000 to 18,000 are born with CAH.

Complications

- Cardiovascular collapse and cardiac arrest (in neonates)
- Hypertension
- Hyperkalemia
- Infertility
- Adrenal tumor

- Altered growth, external genitalia, and sexual maturity

Signs and symptoms

The neonatal female with simple virilizing CAH has ambiguous genitalia (enlarged clitoris, with urethral opening at the base; some labioscrotal fusion) but normal genital tract and gonads. As she grows older, signs of progressive virilization develop: early appearance of pubic and axillary hair, deep voice, acne, and facial hair. The neonatal male with this condition has no obvious abnormality; however, at prepuberty he shows accentuated masculine characteristics, such as deepened voice and an enlarged phallus, with frequent erections. At puberty, females fail to begin menstruation, and males have small testes. Both males and females with this condition may be taller than other children their age as a result of rapid bone and muscle

growth, but because excessive androgen levels hasten epiphyseal closure, abnormally short adult stature results. (See *Acquired adrenal virilism*.)

ACQUIRED ADRENAL VIRILISM

Acquired adrenal virilism results from virilizing adrenal tumors, carcinomas, or adenomas. This rare disorder is twice as common in females as in males. Although acquired adrenal virilism can develop at any age, its clinical effects vary with age at onset:

- Prepubescent females: pubic hair, clitoral enlargement; at puberty, delayed breast development, delayed or absent menses
- Prepubescent males: hirsutism, macrogenitosomia praecox (excessive body development, with marked enlargement of genitalia). Occasionally, the penis and prostate equal those of an adult male in size; however, testicular maturation fails to occur.
- Females (especially middle-aged): dark hair on legs, arms, chest, back, and face; pubic hair extending

toward navel; oily skin, sometimes with acne; menstrual irregularities; muscular hypertrophy (masculine resemblance); male pattern baldness; and atrophy of breasts and uterus
- Males: no overt signs; discovery of tumor usually accidental
- All patients: good muscular development; taller than average during childhood and adolescence; short stature as adults due to early closure of epiphyses.

Diagnosis and treatment

Diagnostic tests for this disorder include:

- Urinary total 17-ketosteroids (17-KS): greatly elevated but levels vary daily; dexamethasone P.O. doesn't suppress 17-KS
- Plasma levels of dehydroepiandrosterone: greatly elevated
- Serum electrolyte levels: normal
- X-ray of kidneys: may show downward displacement of kidneys by tumor.

Treatment requires surgical excision of tumor and metastases (if present), when possible, or radiation therapy and chemotherapy. Preoperative treatment may include glucocorticoids. With treatment, the prognosis is very good in patients with slow-growing and nonrecurring tumors. Periodic follow-up urine testing (for increased 17-KS levels) to check for tumor recurrence is essential.

Salt-losing CAH in females causes more complete virilization than the simple form and results in development of male external genitalia without testes. Because males with this condition have no external genital abnormalities, immediate neonatal diagnosis is difficult, and is commonly delayed until the infant develops severe systemic symptoms. Characteristically, such an infant is apathetic, fails to eat, and has

diarrhea; he develops symptoms of adrenal crisis in the first week of life (vomiting, dehydration from hyponatremia, hyperkalemia). Unless this condition is treated promptly, dehydration and hyperkalemia may lead to cardiovascular collapse and cardiac arrest.

Diagnosis

Physical examination revealing pseudohermaphroditism in females or precocious puberty in both sexes strongly suggests CAH. (See *Hermaphroditism*.)

CONFIRMING DIAGNOSIS

The following laboratory findings confirm the diagnosis: elevated plasma 17-ketosteroids (17-KS), which can be suppressed by administering oral dexamethasone;

elevated urinary levels of hormone metabolites, particularly pregnanetriol; elevated plasma 17-hydroxyprogesterone level; and normal or decreased urinary levels of 17-hydroxycorticosteroids. Elevated dehydroepiandrosterone sulfate is present.

HERMAPHRODITISM

True hermaphroditism (*hermaphrodism, intersexuality*) is a rare condition characterized by the presence of both ovarian and testicular tissues. External genitalia are usually ambiguous but may be completely male or female, thereby masking hermaphroditism until puberty. The hermaphrodite almost always has a uterus (however, fertility is rare) and ambiguous gonads distributed:

- Bilaterally: testis and ovary on both sides, ovotestes
- Unilaterally: ovary or testis on one side, an ovotestis on the other

- Asymmetrically or laterally: an ovary and a testis on opposite sides.

Causes and diagnosis

Because the Y chromosome is needed to develop testicular tissue, hermaphroditism in infants with XY karyotypes is particularly perplexing but may result from mosaicism (XX/XY, XX/XXY), hidden mosaicism, or hidden gene alterations. In patients with XX karyotype, ovaries are usually better developed than in those with XY karyotype. Fifty percent of hermaphrodites have a 46, XX karyotype, 20% have XY, and 30% are mosaics.

Although ambiguous external genitalia suggest hermaphroditism, chromosomal studies (particularly a buccal smear for Barr bodies, indicating an XX karyotype), a 24-hour urine specimen for 17-ketosteroids to rule out congenital adrenal hyperplasia, and gonadal biopsy are necessary to confirm it.

Early treatment crucial

Sexual assignment, based on the anatomy of the external genitalia, and surgical reconstruction should be done as early as possible to prevent physical and psychological consequences of delayed reassignment. During surgery, inappropriate reproductive organs are removed to prevent incongruous secondary sex characteristics at puberty. Hormonal replacement may be necessary.

Nursing intervention emphasizes psychological support of the parents and reinforcement of their choice about sexual assignment.

Adrenal hypofunction or adrenal crisis in the first week of life suggests salt-losing CAH. Hyperkalemia, hyponatremia, and hypochloremia with excessive urinary 17-KS and pregnanetriol and decreased urinary aldosterone levels confirm it.

Treatment

Simple virilizing CAH requires correction of the cortisol deficiency and inhibition of excessive pituitary corticotropin production by daily administration of cortisol. Treatment returns androgen production to normal levels. Measurement of urinary 17-KS levels determines the initial dose of cortisone or hydrocortisone; this dose is usually large and is given I.M. Later dosage is modified according to decreasing urinary 17-KS levels. Infants must continue to receive cortisone or hydrocortisone I.M. until age 18 months; after that, they may take it orally.

PEDIATRIC TIP

The infant with salt-losing CAH in adrenal crisis requires immediate I.V. sodium chloride and glucose infusion to maintain fluid and electrolyte balance and to stabilize vital signs. If saline and glucose infusion doesn't control symptoms while the diagnosis is being established, desoxycorticosterone I.M. and hydrocortisone I.V. are necessary. Later, maintenance includes mineralocorticoid (desoxycorticosterone, fludrocortisone, or both) and glucocorticoid (cortisone or hydrocortisone) replacement.

Sex chromatin and karyotype studies determine the genetic sex of patients with ambiguous external genitalia. Females with masculine external genitalia require reconstructive surgery, such as correction of the labial fusion and of the urogenital sinus. Surgery is usually scheduled between ages 1 and 3, after the effect of cortisone therapy has been assessed.

Special considerations

- Suspect CAH in infants hospitalized for failure to thrive, dehydration, or diarrhea, as well as in tall, sturdy-looking children with a record of numerous episodic illnesses.

- When caring for an infant with adrenal crisis, keep the I.V. line patent, infuse fluids, and give steroids, as ordered. Monitor body weight, blood pressure, and serum electrolyte levels carefully, especially sodium and potassium levels. Watch for cyanosis, hypotension, tachycardia, tachypnea, and signs of shock. Minimize external stressors.
- If the child is receiving maintenance therapy with steroid injections, rotate I.M. injection sites to prevent atrophy; tell parents to do the same. Teach them the possible adverse effects (cushingoid symptoms) of long-term therapy. Explain that maintenance therapy with hydrocortisone, cortisone, or the mineralocorticoid fludrocortisone is essential for life. Warn parents not to withdraw these drugs suddenly because potentially fatal adrenal hypofunction will result. Instruct parents to report stress and infection, which require increased steroid dosages.
- Monitor the patient receiving desoxycorticosterone or fludrocortisone for edema, weakness, and hypertension. Be alert for significant weight gain and rapid changes in height because normal growth is an important indicator of adequate therapy.
- Instruct the patient to wear a medical identification bracelet indicating that she's on prolonged steroid therapy and providing information about dosage.
- Help the parents of a female infant with male genitalia to understand that she's physiologically a female and that this abnormality can be surgically corrected. Arrange for counseling if necessary.

Pheochromocytoma

A pheochromocytoma is a chromaffin-cell tumor of the adrenal medulla that secretes an excess of the catecholamines epinephrine and norepinephrine, resulting in severe hypertension, increased metabolism, and hyperglycemia. This disorder is potentially fatal but the prognosis is generally good with treatment. However, pheochromocytoma-induced kidney damage is irreversible.

Causes and incidence

A pheochromocytoma may result from an inherited autosomal dominant trait. According to some estimates, about 0.5% of newly diagnosed patients with hypertension have pheochromocytoma. While this tumor is usually benign, it may be malignant in as many as 10% of these patients. It affects all races and both sexes, occurring primarily between ages 30 and 40.

Complications

- Stroke
- Retinopathy
- Heart disease
- Irreversible kidney damage

Signs and symptoms

The cardinal sign of pheochromocytoma is persistent or paroxysmal hypertension. Common clinical effects include palpitations, tachycardia, headache, diaphoresis, pallor, warmth or flushing, paresthesia, tremor, excitation, fright, nervousness, feelings of impending doom, abdominal pain, tachypnea, nausea, and vomiting. Orthostatic hypotension and paradoxical response to antihypertensive drugs are common, as are associated glycosuria, hyperglycemia, and hypermetabolism. Patients with hypermetabolism may show marked weight loss but some patients with

pheochromocytomas are obese. Symptomatic episodes may recur as seldom as once every 2 months or as often as 25 times a day. They may occur spontaneously or may follow certain precipitating events, such as postural change, exercise, laughing, smoking, induction of anesthesia, urination, or a change in environmental or body temperature.

Pheochromocytoma is commonly diagnosed during pregnancy, when uterine pressure on the tumor induces more frequent attacks; such attacks can prove fatal for both mother and fetus as a result of a stroke, acute pulmonary edema, cardiac arrhythmias, or hypoxia. In such patients, the risk of spontaneous abortion is high but most fetal deaths occur during labor or immediately after birth.

Diagnosis

The most common presentation for pheochromocytoma is continuous hypertension with or without orthostatic hypotension. A history of acute episodes of hypertension, headache, sweating, and tachycardia—particularly in a patient with hyperglycemia, glycosuria, and hypermetabolism—strongly suggests pheochromocytoma. A patient who has intermittent attacks may have no symptoms during a latent phase. The tumor is rarely palpable; when it is, palpation of the surrounding area may induce an acute attack and help confirm the diagnosis. Generally, diagnosis depends on laboratory findings.

CONFIRMING DIAGNOSIS

Increased urinary excretion of total free catecholamines and their metabolites, vanillylmandelic acid (VMA) and metanephrine, as measured by analysis of a 24-hour urine specimen, confirms pheochromocytoma.

Labile blood pressure necessitates urine collection during a hypertensive episode and comparison of this specimen with a baseline specimen. Direct assay of total plasma catecholamines shows levels 10 to 50 times higher than normal.

Provocative tests with glucagon and phentolamine suggest the diagnosis; however, because they may precipitate a hypertensive crisis or induce a false-positive or false-negative result, they're seldom used. The clonidine suppression test will cause decreased plasma catecholamine levels in normal patients but no change in those with pheochromocytoma. After demonstrating biochemical evidence of pheochromocytoma, computed tomography scan or magnetic resonance imaging of the abdomen (where 95% of pheochromocytomas are located) is warranted. If a tumor isn't located—or if there is more than one—a radioactive iodine metaiodobenzylguanidine scintiscan or nuclear scan usually confirms the diagnosis in unclear cases. Angiography and excretory urography are no longer used; adrenal venography is used, but rarely.

Treatment

Surgical removal of the tumor is the treatment of choice. To decrease blood pressure, an alpha-adrenergic blocker or metyrosine is given from 1 to 2 weeks before surgery. A beta-adrenergic blocker (propranolol) may also be used after achieving alpha blockade. Postoperatively, I.V. fluids, plasma volume expanders, vasopressors and, possibly, transfusions may be required for hypotension. Persistent hypertension in the immediate postoperative period can occur. If surgery isn't feasible, alpha-adrenergic blockers and beta-adrenergic blockers—such as phenoxybenzamine and propranolol, respectively—are beneficial in controlling catecholamine effects and preventing attacks. Management of an acute attack or hypertensive crisis requires I.V. phentolamine (push or drip) or nitroprusside to normalize blood pressure.

Special considerations

To ensure the reliability of urine catecholamine measurements, make sure the patient avoids foods high in vanillin (such as coffee, nuts, chocolate, and bananas) for 2 days before urine collection of VMA. Also, be aware of possible drug therapy that may interfere with the accurate determination of VMA (such as guaifenesin and salicylates). Collect the urine in a special

container, with hydrochloric acid, that has been prepared by the laboratory.

- Obtain blood pressure readings often because transient hypertensive attacks are possible. Tell the patient to report headaches, palpitations, nervousness, or other symptoms of an acute attack. If hypertensive crisis develops, monitor blood pressure and heart rate every 2 to 5 minutes until blood pressure stabilizes at an acceptable level.
- Check blood for glucose, and watch for weight loss from hypermetabolism.
- After surgery, blood pressure may rise or fall sharply. Keep the patient quiet; provide a private room, if possible, because excitement may trigger a hypertensive episode. Postoperative hypertension is common because the stress of surgery and manipulation of the adrenal gland stimulate secretion of catecholamines. Because this excess secretion

causes profuse sweating, keep the room cool, and change the patient's clothing and bedding often. If the patient receives phentolamine, monitor blood pressure closely. Observe and record adverse effects: dizziness, hypotension, and tachycardia. The first 24 to 48 hours immediately after surgery are the most critical because blood pressure can drop drastically.

- If the patient is receiving vasopressors I.V., check blood pressure as per facility protocol or every 15 minutes while titrating, and regulate the drip to maintain a safe pressure. Arterial pressure lines facilitate constant monitoring.
- Watch for abdominal distention and return of bowel sounds.

ALERT

Check dressings and vital signs for indications of hemorrhage (increased pulse rate, decreased blood pressure, cold and clammy skin, pallor, and unresponsiveness).

- Give analgesics for pain, as ordered, but monitor blood pressure carefully because many analgesics, especially meperidine, can cause hypotension.
- If autosomal dominant transmission of pheochromocytoma is suspected, the patient's family should also be evaluated for this condition.

PANCREATIC AND MULTIPLE DISORDERS

Multiple endocrine neoplasia

Multiple endocrine neoplasia (MEN) is a hereditary disorder in which two or more endocrine glands develop hyperplasia, adenoma, or carcinoma, concurrently or consecutively. Two of the types that occur are well documented: MEN I (Werner's syndrome) involves hyperplasia and adenomatosis of the pituitary and parathyroid glands, islet cells of the pancreas and, rarely, the thyroid and adrenal glands; MEN II (Sipple's syndrome) involves medullary carcinoma of the thyroid, with hyperplasia

and adenomatosis of the adrenal medulla (pheochromocytoma) and parathyroid glands. MEN I is the most common form.

Causes and incidence

MEN usually results from autosomal dominant inheritance. It affects males twice as often as females and may occur at any time from adolescence to old age, but is rare in children. There's no racial predilection.

Signs and symptoms

Clinical effects of MEN may develop in various combinations and orders, depending on the glands involved. The most common manifestation of MEN I is hyperparathyroidism, followed by ulcer due to Zollinger-Ellison syndrome (marked by increased gastrin production from non-beta islet cell tumors of the pancreas). Hypoglycemia may result from pancreatic beta islet cell tumors, with increased insulin production. When MEN I affects the parathyroids, it produces signs of hyperparathyroidism, including hypercalcemia (because the parathyroids are primarily responsible for the regulation of calcium and phosphorus levels). When MEN causes pituitary tumor, it's most commonly a prolactinoma, but can be a growth hormone or corticotropin, or even a nonsecretory adenoma.

Characteristic features of MEN II with medullary carcinoma of the thyroid include enlarged thyroid mass, with resultant increased calcitonin and, occasionally, ectopic corticotropin, causing Cushing's syndrome. With tumors of the adrenal medulla, symptoms include headache, tachyarrhythmias, and hypertension; with adenomatosis or hyperplasia of the parathyroids, symptoms result from renal calculi.

Diagnosis

Investigating symptoms of pituitary tumor, hypoglycemia, hypercalcemia, or GI hemorrhage may lead to a diagnosis of MEN. Diagnostic tests must be used to carefully evaluate each affected endocrine gland. For example, radioimmunoassay showing increased levels of gastrin in patients with peptic ulceration and Zollinger-Ellison syndrome suggests the need for follow-up studies for MEN I because 50%

of patients with Zollinger-Ellison syndrome have MEN. After confirmation of MEN, family members must also be assessed for this inherited syndrome.

Magnetic resonance imaging or computed tomography scan of the abdomen may show pancreatic tumor. Insulin test may show increased levels and fasting blood sugar may be low.

Treatment

Treatment must eradicate the tumors. Subsequent therapy controls residual symptoms. In MEN I, peptic ulceration is usually the most urgent clinical feature, so primary treatment emphasizes control of bleeding or resection of necrotic tissue. In hypoglycemia caused by insulinoma, oral administration of diazoxide or glucose can keep blood glucose levels within acceptable limits. Subtotal (partial) pancreatectomy is required to remove the tumor. Because all parathyroid glands have the potential for neoplastic enlargement, subtotal parathyroidectomy may also be required along with transsphenoidal hypophysectomy. In MEN II, treatment of an adrenal medullary tumor includes antihypertensives and resection of the tumor. Bromocriptine may be used for pituitary tumors that secrete prolactin. Hormonal replacement therapy is necessary when glands are removed or secretion is inadequate.

Special considerations

Supportive care depends on the body system involved.

- If MEN involves the pancreas, monitor blood glucose levels frequently. If it affects the adrenal glands, monitor blood pressure closely, especially during drug therapy.
- Manage peptic ulcers, hypoglycemia, and other complications, as needed.
- If pituitary tumor is suspected, watch for signs of pituitary trophic hormone dysfunction, which may affect any of the endocrine glands. Also, be aware that pituitary apoplexy (sudden severe headache, altered level of consciousness, visual disturbances) may occur.

Diabetes mellitus

Diabetes mellitus (DM) is a chronic disease of absolute or relative insulin deficiency or resistance characterized by disturbances in carbohydrate, protein, and fat metabolism. A leading cause of death by disease in the United States, this syndrome is a contributing factor in about 50% of myocardial infarctions and about 75% of strokes as well as in renal failure and peripheral vascular disease. It's also the leading cause of new blindness.

DM occurs in four forms classified by etiology: type 1, type 2, other specific types, and gestational diabetes mellitus (GDM). Type 1 is further subdivided into immune-mediated diabetes and idiopathic diabetes. Those who were previously in the type 1 diabetes group fall into this group. Children and adolescents with type 1 immune-mediated diabetes rapidly develop ketoacidosis, but most adults with this type experience only modest fasting hyperglycemia unless they develop an infection or experience another stressor. Patients with type 1 idiopathic diabetes are prone to ketoacidosis.

Most patients with type 2 diabetes are obese. The “other specific types” category includes people who have diabetes as a result

of a genetic defect, endocrinopathies, or exposure to certain drugs or chemicals. GDM occurs during pregnancy. In this type of diabetes, glucose tolerance levels usually return to normal after delivery.

Causes and incidence

DM affects an estimated 6% of the population of the United States, about half of whom are undiagnosed. Incidence is greater in females and rises with age. Type 2 accounts for 90% of cases.

In type 1 diabetes, pancreatic beta-cell destruction or a primary defect in beta-cell function results in failure to release insulin and ineffective glucose transport. Type 1 immune-mediated diabetes is caused by cell-mediated destruction of pancreatic beta cells. The rate of beta-cell destruction is usually higher in children than in adults. The idiopathic form of type 1 diabetes has no known cause. Patients with this form have no evidence of autoimmunity and don't produce insulin.

In type 2 diabetes, beta cells release insulin, but receptors are insulin-resistant and glucose transport is variable and ineffective. Risk factors

for type 2 diabetes include:

- obesity (even an increased percentage of body fat primarily in the abdominal region); risk decreases with weight and drug therapy
- lack of physical activity
- history of GDM
- hypertension
- Black, Hispanic, Pacific Islander, Asian American, Native American origin
- strong family history of diabetes
- older than age 45
- high-density lipoprotein cholesterol of less than 35 or triglyceride of greater than 250
- Seriously impaired glucose tolerance (IGT) test.

ELDER TIP

As the body ages, the cells become more resistant to insulin, thus reducing the older adult's ability to metabolize glucose. In addition, the release of insulin from the pancreatic beta cells is reduced and delayed. These combined processes result in hyperglycemia. In the older patient, sudden concentrations of glucose cause increased and more prolonged hyperglycemia.

The “other specific types” of DM result from various conditions (such as a genetic defect of the beta cells or endocrinopathies) or from use of or exposure to certain drugs or chemicals. GDM is considered present whenever a patient has any degree of abnormal glucose during pregnancy. This form may result from weight gain and increased levels of estrogen and placental hormones, which antagonize insulin.

Insulin transports glucose into the cell for use as energy and storage as glycogen. It also stimulates protein synthesis and free fatty acid storage in the fat deposits. Insulin deficiency compromises the body tissues' access to essential nutrients for fuel and storage.

Complications

- Cardiovascular disease
- Peripheral vascular disease
- Retinopathy
- Nephropathy
- Susceptibility to skin and urinary tract infections and vaginitis

Signs and symptoms

Diabetes may begin dramatically with ketoacidosis or insidiously. Its most common symptom is fatigue from energy deficiency and a catabolic state. Insulin deficiency causes hyperglycemia, which pulls fluid from body tissues, causing osmotic diuresis, polyuria, dehydration, polydipsia, dry mucous membranes, poor skin turgor and, in most patients, unexplained weight loss.

ELDER TIP

Because their thirst mechanism functions less effectively, older adults may not report polydipsia, a hallmark of diabetes in younger adults.

In ketoacidosis and hyperosmolar hyperglycemic nonketotic syndrome, dehydration may cause hypovolemia and shock. Wasting of glucose in the urine usually produces weight loss and hunger in type 1 diabetes, even if the patient eats voraciously. (See *Understanding ketoacidosis and hyperosmolar coma*, pages 646 and 647.)

Long-term effects of diabetes may include retinopathy, nephropathy, atherosclerosis,

and peripheral and autonomic neuropathy. Peripheral neuropathy usually affects the hands and feet and may cause numbness or pain. Autonomic neuropathy may manifest itself in several ways, including gastroparesis (leading to delayed gastric emptying and a feeling of nausea and fullness after meals), nocturnal diarrhea, impotence, and orthostatic hypotension.

Because hyperglycemia impairs the patient's resistance to infection, diabetes may result in skin and urinary tract infections (UTIs) and vaginitis. Glucose content of the epidermis and urine encourages bacterial growth.

Diagnosis

According to the American Diabetes Association (ADA), DM can be diagnosed if any of the following exist:

- symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus a random (non-fasting) blood glucose level greater than or equal to 200 mg/dl accompanied by symptoms of diabetes.
- a fasting blood glucose level (no caloric intake for at least 8 hours) greater than or equal to 126 mg/dl.
- a plasma glucose value in the 2-hour sample of the oral glucose tolerance test greater than or equal to 200 mg/dl. This test should be performed after a glucose load dose of 75 g of anhydrous glucose.

If results are questionable, the diagnosis should be confirmed by a repeat test on a different day. The ADA also recommends the following testing guidelines:

- Test every 3 years: people age 45 or older without symptoms
- Test immediately: people with the classic symptoms
- High-risk groups should be tested frequently: Individuals with impaired glucose tolerance usually have normal blood levels unless challenged by a glucose load, such as a piece of pie or glass of orange juice. Two hours after a glucose load, the glucose level ranges from 140 to 199 mg/dl. These individuals have an abnormal fasting glucose level between 110 and 125 mg/dl. Because the fasting plasma glucose test is sufficient to make the diagnosis of diabetes, it replaces the oral glucose tolerance test. (See *Classifying blood glucose levels.*)

CLASSIFYING BLOOD GLUCOSE LEVELS

The American Diabetes Association classifies fasting blood glucose levels as follows.

- Normal: < 100 mg/dl

- Prediabetes: 100 to 125 mg/dl
- Diabetes: ≥ 126 mg/dl

An ophthalmologic examination may show diabetic retinopathy. Other diagnostic and monitoring tests include urinalysis for acetone and blood testing for glycosylated hemoglobin (Hb A_{1C}), which reflects recent glucose cortisol.

Treatment

Effective treatment normalizes blood glucose and decreases complications using insulin replacement, diet, and exercise. Current forms of insulin replacement include single-dose, mixed-dose, split-mixed dose, and multiple-dose regimens. The multiple-dose regimens may use an insulin pump. Insulin may be rapid acting, intermediate acting, long acting, or a combination of rapid acting and intermediate acting; it may be standard or purified, and it may be derived from beef, pork, or human sources. Purified human insulin is used commonly today. Pancreas transplantation is experimental and requires chronic immunosuppression.

Successful treatment requires an extensive dietary education. The patient's diet is specifically tailored to include the right amount and combination of foods. Almost all foods may be eaten occasionally. The diet should address dietary prescriptions as well as personal and cultural preferences to improve adherence and control. For the obese patient with type 2 diabetes, weight reduction is a goal. In type 1 diabetes, the calorie allotment may be high, depending on growth stage and activity level.

Type 2 diabetes may require oral antidiabetic drugs to stimulate endogenous insulin

production, increase insulin sensitivity at the cellular level, and suppress hepatic gluconeogenesis.

PATHOPHYSIOLOGY
UNDERSTANDING KETOACIDOSIS AND HYPEROSMOLAR COMA

Ketoacidosis and hyperosmolar coma are acute complications of hyperglycemic crisis that may occur in a patient with diabetes. If not treated properly, either may result in coma or death.

Ketoacidosis is most common in patients with type 1 diabetes; in fact, it may be the first evidence of previously unrecognized type 1 diabetes. Although hyperosmolar coma is most common in patients with type 2 diabetes, it may also occur in anyone whose insulin tolerance is stressed and in patients who have undergone certain therapeutic procedures, such as peritoneal dialysis, hemodialysis, tube feedings, or total parenteral nutrition.

Acute insulin deficiency (absolute in ketoacidosis; relative in hyperosmolar coma) precipitates both conditions. Causes include illness, stress, infection, and failure to take insulin (only in a patient with ketoacidosis).

Buildup of glucose

Inadequate insulin hinders glucose uptake by fat and muscle cells. Because the cells can't take in glucose to convert to energy, glucose accumulates in the blood. At the same time, the liver responds to the demands of the energy-starved cells by converting glycogen to glucose and releasing glucose into the blood, *further* increasing the blood glucose level. When this level exceeds the renal threshold, excess glucose is excreted in the urine.

Still, the insulin-deprived cells can't use glucose. Their response is rapid metabolism of protein, which results in loss of intracellular potassium and phosphorus and in excessive

liberation of amino acids. The liver converts these amino

acids into urea and glucose.

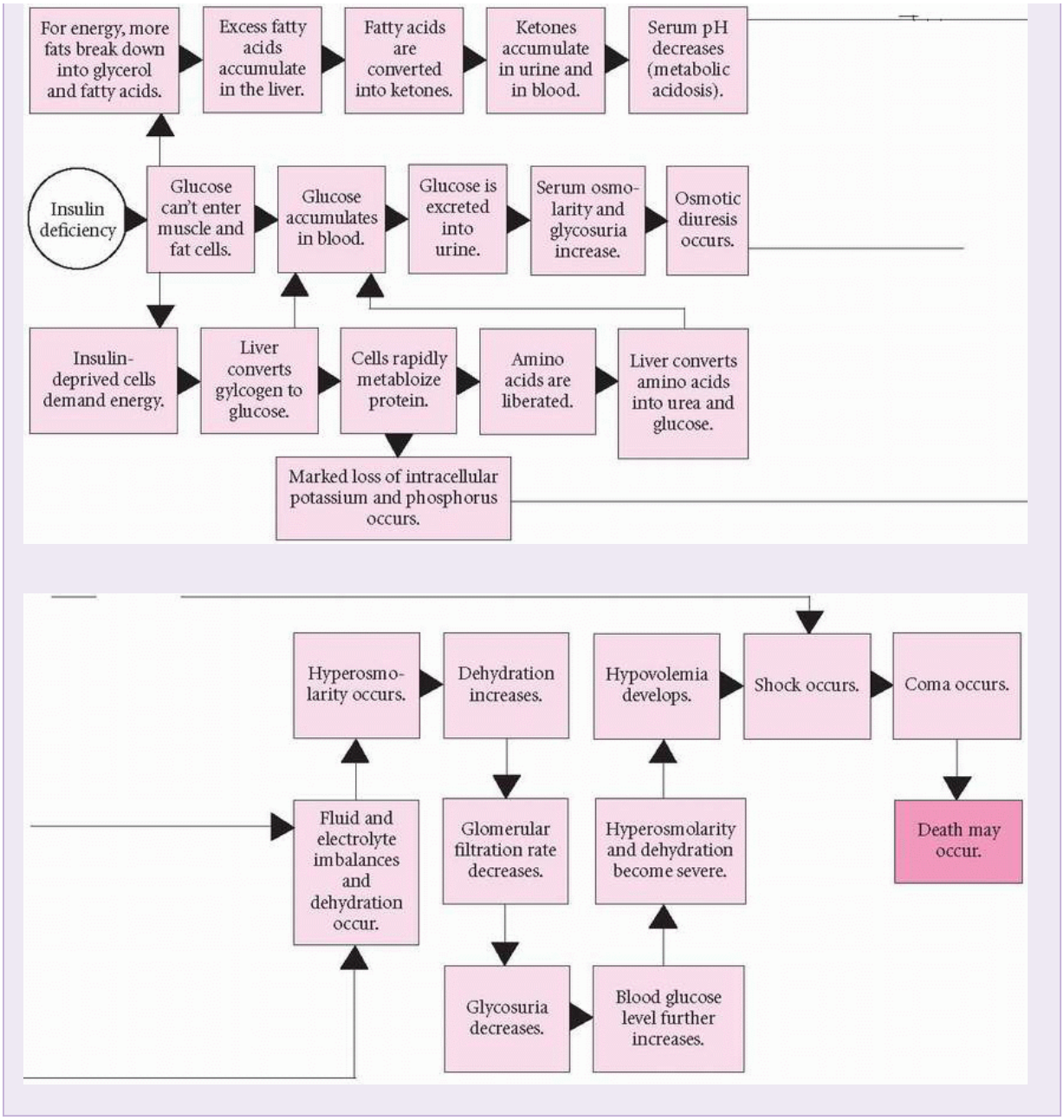
As a result of these processes, the blood glucose level is grossly elevated. The aftermath is increased serum osmolarity and glycosuria (higher in patients with hyperosmolar coma than in those with ketoacidosis because the blood glucose level is higher in those with hyperosmolar coma), leading to osmotic diuresis.

A deadly cycle

The massive fluid loss from osmotic diuresis causes fluid and electrolyte imbalances and dehydration. Water loss exceeds electrolyte loss, contributing to hyperosmolarity. This, in turn, perpetuates dehydration, decreasing the glomerular filtration rate and reducing the amount of glucose excreted in the urine, leading to a deadly cycle: Diminished glucose excretion *further* raises the blood glucose level, producing severe hyperosmolarity and dehydration and finally causing shock, coma, and death.

Further ketoacidosis complication

All these steps hold true for both ketoacidosis and hyperosmolar coma. But ketoacidosis has an additional simultaneous process that leads to metabolic acidosis. The absolute insulin deficiency causes cells to convert fats into glycerol and fatty acids for energy. The fatty acids can't be metabolized as quickly as they're released, so they accumulate in the liver, where they're converted into ketones (ketoacids). These ketones accumulate in the blood and urine and cause acidosis. Acidosis leads to more tissue breakdown, more ketosis, more acidosis, and eventually shock, coma, and death.



Many types of drugs have been used to treat diabetes. Sulfonylureas stimulate pancreatic insulin release, increase tissue sensitivity to insulin, and require insulin's presence to work. Meglitinides cause immediate, brief release of insulin and are taken immediately before meals. Biguanides decrease hepatic glucose production and increase tissue sensitivity to insulin. Alpha-glucosidase inhibitors slow the breakdown of glucose and decrease postprandial glucose peaks. The thiazolidinediones enhance the action of insulin; however, insulin must

be present for them to work. These drugs also reduce insulin resistance by decreasing hepatic glucose production and increasing glucose uptake. They have also been shown to lower blood pressure in diabetic hypertensive patients. Cholesterol and triglyceride levels may also be reduced.

A new class of anti-hyperglycemics, which is a synthetic analogue of human amylin, helps control glucose. Amylin is absent in patients with diabetes. When used with insulin, this synthetic hormone can improve glycemic control by eliminating postprandial glucose level peaks.

Combination drugs, such as Glyburide and Metformin (Glucotrol) are also available that combine varying doses of two types of diabetes drugs allowing the patient to take fewer pills. These are frequently prescribed once the patient is stable on individual drugs for awhile.

Treatment of long-term diabetic complications may include transplantation or dialysis for renal failure, photocoagulation for retinopathy, and vascular surgery for large-vessel disease. Meticulous blood glucose control is essential.

ALERT

Any patient with a wound that has lasted more than 8 weeks and who has tried standard wound care and revascularization without improvement should consider hyperbaric oxygen therapy. This treatment may speed healing by allowing more oxygen to get to the wound and may therefore result in fewer amputations.

Keeping glucose at near-normal levels for 5 years or more reduces both the onset and progression of retinopathy, nephropathy, and neuropathy. In type 2 diabetes, blood pressure control as well as smoking cessation reduces the onset and progression of complications, including cardiovascular disease. (See Insulin therapy.*)*

Special considerations

Stress the importance of complying with the prescribed treatment program. Tailor your teaching to the patient's needs, abilities, and developmental stage. Include diet; purpose, administration, and possible

adverse effects of medication; exercise; monitoring; hygiene; and the prevention and recognition of hypoglycemia and hyperglycemia. Stress the effect of blood glucose control on long-term health. (See *Preventing diabetes complications*, page 650.)

ALERT

Watch for acute complications of diabetic therapy, especially hypoglycemia (vagueness, slow cerebration, dizziness, weakness, pallor, tachycardia, diaphoresis, seizures, and coma); immediately give carbohydrates, ideally in the form of glucose tablets, honey, or fruit juice. If the patient is unconscious, give glucagon or dextrose I.V. Check glucose level every 20 minutes and repeat glucose tablets until glucose level exceeds 120 mg/dl or meets institutional policy.

ALERT

Be alert for signs of ketoacidosis (acetone breath, dehydration, weak and rapid pulse, and Kussmaul's respirations) and hyperosmolar coma (polyuria, thirst, neurologic abnormalities, and stupor). These hyperglycemic crises require I.V. fluids, insulin and, usually, potassium replacement.

- Monitor diabetes control by obtaining blood glucose, glycohemoglobulin, lipid levels, and blood pressure measurements regularly.
- Watch for diabetic effects on the cardiovascular system, such as cerebrovascular, coronary artery, and peripheral vascular impairment, and on the peripheral and autonomic nervous systems. Treat all injuries, cuts, and blisters (particularly on the legs or feet) meticulously. Be alert for signs of UTI and renal disease.
- Urge regular ophthalmologic examinations to detect diabetic retinopathy.

- Assess for signs of diabetic neuropathy (numbness or pain in hands and feet, footdrop, neurogenic bladder). Stress the need for personal safety precautions because decreased sensation can mask injuries. Minimize complications by maintaining strict blood glucose control.
- Teach the patient to care for his feet by washing them daily, drying carefully between toes, and inspecting for corns, calluses, redness, swelling, bruises, and breaks in the skin. Urge him to report changes to the physician. Advise him to wear nonconstricting shoes and to avoid walking barefoot. Instruct him to use over-the-counter athlete's foot remedies and seek professional care should athlete's foot not improve.
- Teach the patient how to manage his diabetes when he has a minor illness, such as a cold, flu, or upset stomach.
- To delay the clinical onset of diabetes, teach people at high risk to avoid risk factors. Advise genetic counseling for young adult diabetics who are planning families.
- Further information may be obtained from the Juvenile Diabetes Foundation, the ADA, and the American Association of Diabetes Educators.

INSULIN THERAPY

Insulin is administered as prescribed. There are several routes of administration and devices for injection.

Subcutaneous route

Insulin is usually given by subcutaneous (SubQ) injection with a standard insulin syringe. SubQ insulin can also be given with a penlike injection device that uses a disposable needle and replaceable insulin cartridges, eliminating the need to draw insulin into a syringe.

Jet-injection devices

Jet-injection devices are expensive and require special cleaning procedures, but they disperse insulin more rapidly and speed absorption. These devices draw up insulin from standard containers, which enables the

patient to mix insulins, if necessary, but requires a special procedure for drawing it up. After the insulin is drawn up, it's delivered into the subcutaneous tissue with a pressure jet.

Insulin pumps

Multiple-dose regimens may use an insulin pump to deliver insulin continuously into subcutaneous tissue. The infusion rate selector automatically releases about half of the total daily insulin requirement evenly over 24 hours. The patient releases the remainder in bolus amounts before meals and snacks.

Site rotation

When administering insulin injections SubQ, the injection sites should be rotated. Because absorption rates differ at each site, diabetic educators recommend rotating the injection site within a specific area such as the abdomen.

I.V. and I.M. routes

Regular insulin or insulin lispro may also be administered I.M. or I.V. during severe episodes of hyperglycemia. These are the only types of insulin that should ever be administered by these routes.

Aerosolized insulin

Intranasal administration uses aerosolized insulin combined with a surfactant; it's administered as a nasal spray. Because nasal solutions are less potent than SubQ insulin, dosages are higher. Insulin inhalers are now available and can be used alone to administer insulin or may be used in combination with other oral insulins for better glucose control.

PREVENTION

PREVENTING DIABETES COMPLICATIONS

Although diabetes mellitus itself cannot be prevented, several things can be done to prevent serious complications, such as blindness, kidney damage, and limb amputations.

Managing glucose

- Managing glucose level is important for preventing complications because wildly fluctuating blood glucos levels place the patient at much higher risk. High levels of glucose can cause arteriosclerosis, which can lead to heart attack and stroke. By exercising and maintaining blood sugar at or near normal levels, the risk can be reduced.
- High glucose level can cause blockage of the small blood vessels that supply the limbs with blood. This can cause nerve damage with a loss of sensation. In addition, the patient with diabetes has slow tissue repair which makes them more prone to infections and amputation of the limbs. The patient with diabetes should never walk around barefoot. Even the smallest cut can cause problems.
- Following the prescribed diet (with weight loss if needed), medication regimen (if prescribed), and the recommended exercise program should be the keys to controlling glucose levels.

Managing blood pressure

- Because elevated glucose level causes elevated blood pressure, the patient with diabetes who also has hypertension is at greater risk for developing kidney disease. The continuing high blood pressure can damage the kidney's filtration mechanism and cause kidney failure.

- Blood pressure control can reduce heart disease and stroke by about one-third to one-half and can reduce eye, kidney, and nerve disease by about a third.

Preventive care

- The patient with diabetes should check his feet every day for swelling, redness, and warmth. These are signs that he should notify his practitioner immediately. In addition, the patient should have his feet checked at least once a year by his practitioner.
- Diabetes can damage the retina of the eye, called retinal neuropathy, which can lead to blindness. Eye examinations should be done once a year and any blurred vision should be reported to the practitioner immediately.

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