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Metabolic and nutritional disorders

Introduction

Metabolism is the physiologic process that allows cells to transform food into energy and continually rebuild body cells. Metabolism has two phases: catabolism and anabolism. In *catabolism,* the energyproducing phase of metabolism, the body breaks down large food molecules into smaller ones; in *anabolism,* the tissue-building phase, the body converts small molecules into larger ones (such as antibodies to keep the body capable of fighting infection). Both phases are accomplished by means of a chemical process using energy. A wide range of nutrients is metabolized to meet the body's needs. (See *Essential nutrients and their functions*.)

ELDER TIP

A person's protein, vitamin, and mineral requirements usually remain the same as he ages, although calorie needs decline. Diminished activity may lower energy requirements by almost 200 calories per day for men and women ages 51 to 75, 400 calories per day for women older than age 75, and 500 calories per day for men older than age 75.

Carbohydrates: Primary energy source

The body gets most of its energy by metabolizing carbohydrates, especially glucose. Glucose catabolism proceeds in three phases:

- *Glycolysis,* a series of chemical reactions, converts glucose molecules into pyruvic or lactic acid.
- The *citric acid cycle* removes ionized hydrogen atoms from pyruvic acid and produces carbon dioxide.
- *Oxidative phosphorylation* traps energy from the hydrogen electrons and combines the hydrogen ions and electrons with oxygen to form water and the common form of biologic energy, adenosine triphosphate (ATP).

Other essential processes in carbohydrate metabolism include glycogenesis— the formation of glycogen, a storage form of glucose— which occurs when cells become saturated with glucose-6-phosphate (an intermediate product of glycolysis); glycogenolysis, the reverse process, which converts glycogen into glucose-6-phosphate in muscle cells and liberates free glucose in the liver; and gluconeogenesis, or “new” glucose formation from protein amino acids or fat glycerols.

A complex interplay of hormonal and neural controls regulates glucose metabolism. Hormone secretions of five endocrine glands dominate this regulatory function:

- Alpha cells of the islets of Langerhans secrete glucagon, which increases the blood glucose level by stimulating phosphorylase activity to accelerate liver glycogenolysis.
- Beta cells of the islets of Langerhans secrete the glucose-regulating hormone insulin, which assists in glucose transport across cell membranes and storage of excess glucose as fat.
- The adrenal medulla, as a physiologic response to stress, secretes epinephrine, which stimulates liver and muscle glycogenolysis to increase the blood glucose level.
- Corticotropin and glucocorticoids also increase blood glucose levels. Glucocorticoids accelerate gluconeogenesis by promoting the flow of amino acids to the liver, where they're synthesized into glucose.
- Human growth hormone (hGH) limits the fat storage and favors fat catabolism; consequently, it inhibits carbohydrate catabolism and thus raises blood glucose levels.

- Thyroid-stimulating hormone and thyroid hormone have mixed effects on carbohydrate metabolism and may raise or lower blood glucose levels.

Fats: Catabolism and anabolism

The breaking up of triglycerides—*lipolysis* —yields fatty acids and glycerol. Betaoxidation breaks down fatty acids into acetyl coenzyme A, which can then enter the citric acid cycle; glycerol can also undergo gluconeogenesis or enter the glycolytic pathways to produce energy. Conversely, *lipogenesis* is the chemical formation of fat from excess carbohydrates and proteins or from the fatty acids and glycerol products of lipolysis. Adipose tissue is the primary storage site for excess fat and thus is the greatest source of energy reserve. Certain unsaturated fatty acids are necessary for synthesis of vital body compounds.

Because the body can't produce these essential fatty acids, they must be provided through diet. Insulin, hGH, catecholamines, corticotropin, and glucocorticoids control fat metabolism in an inverse relationship with carbohydrate metabolism; large amounts of carbohydrates promote fat storage, and deficiency of available carbohydrates promotes fat breakdown for energy needs.

ESSENTIAL NUTRIENTS AND THEIR FUNCTIONS

Nutrients are required for the body to work properly and avoid disease.

Nutrients	Functions
Carbohydrates	▪ Energy source
Fats and essential fatty acids	▪ Energy source; essential for growth, normal skin, and membranes
Proteins and amino acids	▪ Synthesis of all body proteins, growth, and tissue maintenance
Water-soluble	

vitamins:	
▪ Ascorbic acid (C)	▪ Collagen synthesis, wound healing, antioxidation
▪ Thiamine (B_1)	▪ Coenzyme in carbohydrate metabolism
▪ Riboflavin (B_2)	▪ Coenzyme in energy metabolism
▪ Niacin	▪ Coenzyme in carbohydrate, fat, energy metabolism, and tissue metabolism
▪ Vitamin B_{12}	▪ Deoxyribonucleic acid (DNA) and ribonucleic acid synthesis; erythrocyte formation
▪ Folic acid	▪ Coenzyme in amino acid metabolism; heme and hemoglobin formation; DNA synthesis; lowering homocysteine levels
Fats soluble vitamins:	
▪ Vitamin A	▪ Vision in dim light, mucosal epithelium integrity, tooth development, endocrine function
▪ Vitamin D	▪ Regulation of calcium and phosphate absorption and metabolism; renal phosphate clearance
▪ Vitamin E	▪ Antioxidation; essential for muscle, liver, and red blood cell integrity
▪ Vitamin K	▪ Blood clotting (catalyzes synthesis of prothrombin by liver)

Proteins: Anabolism

The primary process in protein metabolism is anabolism. Catabolism is relegated to a supporting role in protein metabolism —a reversal of the roles played by these two processes in carbohydrate and fat metabolisms. By synthesizing proteins— the tissue-building foods—the body derives substances essential for life (such as plasma proteins) and can reproduce, control cell growth, and repair itself. However, when carbohydrates or fats are unavailable as energy sources, or when energy

demands are exceedingly high, protein catabolism converts protein into an available energy source. Protein metabolism consists of many processes, including:

- *Deamination* — a catabolic and energyproducing process occurring in the liver with the splitting off of the amino acid to form ammonia and a keto acid
- *Transamination* — anabolic conversion of keto acids to amino acids
- *Urea formation* — a catabolic process occurring in the liver, producing urea, the end product of protein catabolism.

The male hormone testosterone and hGH stimulate protein anabolism; corticotropin prompts secretion of glucocorticoids, which, in turn, facilitate protein catabolism. Normally, the rate of protein anabolism equals the rate of protein catabolism —a condition known as *nitrogen balance* (because ingested nitrogen equals nitrogen waste excreted in urine, feces, and sweat). When excessive catabolism causes the amount of nitrogen excreted to exceed the amount ingested, a state of *negative nitrogen balance* exists—usually the result of starvation and cachexia or surgical stress.

Fluid and electrolyte balance

A critical component of metabolism is fluid and electrolyte balance. Water is an essential body substance and constitutes almost 60% of an adult's body weight and more than 75% of a neonate's body weight. In both older and obese adults, the ratio of water to body weight drops; children and lean people have a higher proportion of water in their bodies.

Body fluids can be classified as intracellular (or cellular) or extracellular. Intracellular fluid constitutes about 40% of total body weight and 60% of all body fluid; it contains large quantities of potassium and phosphates but very little sodium and chloride. Conversely, extracellular fluid (ECF) contains mostly sodium and chloride but very little potassium and phosphates. Incorporating interstitial, cerebrospinal, intraocular, and GI fluids and plasma, ECF supplies cells with nutrients and other substances needed for cellular function. The many components of body fluids have

the important function of preserving osmotic pressure and acid-base and anion-cation balance.

Homeostasis is a stable state—the equilibrium of chemical and physical properties of body fluid. Body fluids contain two kinds of dissolved substances: those that dissociate in solution (electrolytes) and those that don't. For example, glucose, when dissolved in water, doesn't break down into smaller particles; but sodium chloride dissociates in solution into sodium cations (+) and chloride anions (-). The composition of these electrolytes in body fluids is electrically balanced so the positively charged ions (cations: sodium, potassium, calcium, and magnesium) equal the negatively charged ions (anions: chloride, bicarbonate, sulfate, phosphate, proteinate, and carbonic and other organic acids). Although these particles are present in relatively low concentrations, any deviation from their normal levels can have profound physiologic effects.

ELDER TIP

Institutionalized older people are at particularly high risk for dehydration because of their diminished thirst perception and any combination of physical, cognitive, speech, mobility, and visual impairment.

In homeostasis—an ever-changing but balanced state—water and electrolytes and other solutes move continually between cellular and extracellular compartments. Such motion is made possible by semipermeable membranes that allow diffusion, filtration, and active transport. Diffusion refers to the movement of particles or molecules from an area of greater concentration to one of lesser concentration. Normally, particles move randomly and constantly until the concentrations within given solutions are equal. Diffusion also depends on permeability, electrical gradient, and pressure gradient. Particles, however, can't diffuse against any of these gradients without energy and a carrier substance (active transport). ATP is released from cells to aid particles needing energy to pass through the cell membrane.

The diffusion of water from a solution of low concentration to one of high concentration is called osmosis. The pressure that develops when a selectively permeable cell membrane separates solutions of different strengths of concentrations is known as *osmotic pressure*, expressed in

terms of osmols or milliosmols (mOsm). Osmotic activity is described in terms of *osmolality* — the osmotic pull exerted by all particles per unit of water, expressed in mOsm/ kg of water—or *osmolarity,* when expressed in mOsm/L of solution.

The normal range of body fluid osmolality is 285 to 295 mOsm/kg. Solutions of 50 mOsm above or below the high and low points of this normal range exert little or no osmotic effect (isosmolality). A solution below 240 mOsm contains a lower

particle concentration than plasma (hypoosmolar) while a solution over 340 mOsm has a higher particle concentration than plasma (hyperosmolar).

Rapid I.V. administration of isosmolar solutions to patients who are debilitated, are very old or very young, or have cardiac or renal insufficiency could lead to ECF volume overload and induce pulmonary edema and heart failure because particulate concentration is the same as plasma, so fluid shifting into and out of cells will occur.

Continuous I.V. administration of hypoosmolar solutions decreases serum osmolality and leads to excess intracellular fluid volume (water intoxication), whereas continuous I.V. administration of hyperosmolar solutions results in intracellular dehydration, increased serum osmolality and, eventually, ECF volume deficit due to excessive urinary excretion. These states occur because of fluid diffusion and the cell's attempt to balance the particulate concentrations inside and outside the cell.

Regulation of pH

Primarily through the complex chemical regulation of carbonic acid by the lungs and of base bicarbonate by the kidneys, the body maintains the hydrogen ion concentration to keep the ECF pH between 7.35 and 7.45. Nutritional deficiency or excess, disease, injury, or metabolic disturbance can interfere with normal homeostatic mechanisms and raise pH (acidosis) or lower it (alkalosis).

Assessing homeostasis

The goal of metabolism and homeostasis is to maintain the complex environment of ECF—the plasma—which nourishes and supports every

body cell. This special environment is subject to multiple interlocking influences and readily reflects any disturbance in nutrition, chemical or fluid content, and osmotic pressure. Such disturbances can be detected by various laboratory tests. For example, measurements of albumin, prealbumin, and other blood proteins; electrolyte concentration; enzyme and antibody levels; and urine and blood chemistry levels (lipoproteins, glucose, blood urea nitrogen [BUN], creatinine, and creatinine-height index) accurately reflect the state of metabolism, homeostasis, and nutrition throughout the body. (See *Laboratory tests: Assessing nutritional status,* page 546.) Results of such laboratory tests, of course, supplement the information obtained from dietary history and physical examination—which offer gross clinical information about the quality, quantity, and efficiency of metabolic processes. To support clinical information, anthropometry, height-weight ratio, and skin-fold thickness determinations specifically define tissue nutritional status.

The following measures can help you maintain your patient's homeostasis.

- Obtain a complete dietary history and nutritional assessment to determine if carbohydrate, fat, protein, vitamin, mineral, and water intake are adequate for energy production and for tissue repair and growth. Remember that during periods of rapid tissue synthesis (growth, pregnancy, healing), protein needs increase.
- Consult a dietitian about any patient who may be malnourished because of malabsorption syndromes, renal or hepatic disease, clear-liquid diets, or who may possibly receive nothing by mouth for more than 5 days. Planned meals that provide adequate carbohydrates, fats, and protein are necessary for convalescence. Supplementary carbohydrates are often needed to spare protein and achieve a positive nitrogen balance.
- Accurately record intake and output to assess fluid balance (this includes intake of oral liquids or I.V. solutions, and urine, gastric, and stool output).
- Weigh the patient daily—at the same time, with the same-type clothing, and on the same scale. Remember, a weight loss of 2.2 lb (1 kg) is equivalent to the loss of 1 L of fluid.

- Observe the patient closely for insensible water or unmeasured fluid losses (such as through diaphoresis). Remember, fluid loss from the skin and lungs (normally 900 ml/ day) can reach as high as 2,000 ml/day from hyperventilation or tachypnea, thus increasing insensible water losses.

ELDER TIP

Teach elderly patients and others vulnerable to fluid imbalances the importance of maintaining adequate fluid intake.

LABORATORY TESTS: ASSESSING NUTRITIONAL STATUS

Blood and urine tests provide the most precise data about nutritional status, often revealing nutritional problems before they're clinically apparent. The list below explains some common tests and what their results mean.

Serum vitamins and minerals

Vitamin and mineral deficiencies commonly screened for include A, B, B_{12}, folic acid, ascorbic acid, beta carotene, riboflavin and, sometimes, zinc, calcium, magnesium, iron, and other minerals.

Serum nutrients

Glucose levels help assess suspected diabetes or hypoglycemia. Cholesterol and triglyceride levels help differentiate the type of hyperlipoproteinemia.

Nitrogen balance

A negative nitrogen balance indicates inadequate intake of protein or calories.

Hemoglobin and hematocrit

Decreased levels can occur in protein-calorie malnutrition, iron deficiency, overhydration, hemorrhage,

and hemolytic disease; elevated levels in dehydration, polycythemia, and folate and B_{12} deficiency.

Serum albumin

Reduced levels may indicate overhydration or visceral protein depletion because of GI disease, liver disease, or nephrotic syndrome. Elevated levels occur in dehydration.

Delayed hypersensitivity skin testing

One or more positive responses, in 24 to 48 hours, to intradermally injected common recall antigens indicates intact cell-mediated immunity. Negative, delayed, or absent response may indicate protein-calorie malnutrition but may also be seen in patients on steroids or with cancer, as well as patients with shock or sepsis.

Creatinine-height index (CHI)

This calculated value reflects muscle mass and estimates muscle protein depletion. Reduced CHI may indicate protein-calorie malnutrition or impaired renal function.

Serum prealbumin

This carrier protein for thyroxine is a sensitive indicator of visceral protein.

Total lymphocyte count

This provides an indication of immune status. Counts are low in malnutrition and acquired immunodeficiency syndrome.

- Recognize I.V. solutions that are hyposmolar, such as 0.45% NaCl (half-normal saline solution). Isosmolar solutions include normal saline solution (0.9% NaCl), 5% dextrose in 0.2% NaCl, Ringer's solutions, and 5% dextrose in water. (The latter acts like a hypotonic solution because dextrose is quickly metabolized, leaving only free water.) Hyperosmolar solutions include 5% dextrose in normal saline solution, 10% dextrose in water, and 5% dextrose in Ringer's lactate solution.

- When continuously administering hypoosmolar solutions, watch for signs of water intoxication: headaches, behavior changes (confusion or disorientation), nausea, vomiting, rising blood pressure, and falling pulse rate.
- When continuously administering hyperosmolar solutions, be alert for signs of hypovolemia: thirst, dry mucous membranes, slightly falling blood pressure, rising pulse rate and respirations, low-grade fever (99° F [37.2° C]), and elevated hematocrit, hemoglobin, and BUN levels.
- Administer fluid cautiously, especially to the patient with cardiopulmonary or renal disease, and watch for signs of overhydration:

  constant and irritating cough, dyspnea, moist crackles, rising central venous pressure, and pitting edema (late sign). When the patient is in an upright position, neck and hand vein engorgement is a sign of fluid overload.

ELDER TIP

Many older patients take drugs to treat a variety of conditions. Remember that drugs can affect the patient's nutritional status by altering nutrient absorption, metabolism, utilization, or excretion. Likewise, various foods, beverages, and mineral or vitamin supplements can affect the absorption and effectiveness of drugs. Be aware of these potential interactions when evaluating the patient's medication regimen and nutritional status.

NUTRITIONAL IMBALANCE

Vitamin A deficiency

A fat-soluble vitamin absorbed in the GI tract, vitamin A maintains epithelial tissue and retinal function. Consequently, deficiency of this vitamin may result in night blindness, decreased color adjustment, keratinization of epithelial tissue, and poor bone growth. Healthy adults

have adequate vitamin A reserves to last up to a year; children often don't.

Causes and incidence

Vitamin A deficiency usually results from inadequate intake of foods high in vitamin A (liver, kidney, butter, milk, cream, cheese, and fortified margarine) or carotene, a precursor of vitamin A found in dark green leafy vegetables and yellow or orange fruits and vegetables. (Six mg of beta-carotene is equal to 1 mg of vitamin A.) The recommended daily allowance for vitamin A is 1 mg for adult males and 0.8 mg for adult females.

Less common causes include:

- malabsorption due to celiac disease, sprue, cirrhosis, obstructive jaundice, cystic fibrosis, giardiasis, or habitual use of mineral oil as a laxative
- massive urinary excretion caused by cancer, tuberculosis, pneumonia, nephritis, or urinary tract infection
- decreased storage and transport of vitamin A due to hepatic disease.

Each year, more than 80,000 people worldwide—mostly children in underdeveloped countries—lose their sight from severe vitamin A deficiency. This condition is rare in the United States, although many disadvantaged children have substandard levels of vitamin A. With therapy, the chance of reversing symptoms of night blindness and milder conjunctival changes is excellent. When corneal damage is present, emergency treatment is necessary.

Complication

- Corneal damage

Signs and symptoms

Typically, the first symptom of vitamin A deficiency is night blindness (nyctalopia), which usually becomes apparent when the patient enters a dark place or is caught in the glare of oncoming headlights while driving at night. This condition can progress to xerophthalmia, or drying of the

conjunctivas, with development of gray plaques (Bitot's spots); if unchecked, perforation, scarring, and blindness may result. Keratinization of epithelial tissue causes dry, scaly skin; follicular hyperkeratosis; and shrinking and hardening of the mucous membranes, possibly leading to infections of the eyes and the respiratory or genitourinary tract. An infant with severe vitamin A deficiency shows signs of failure to thrive and apathy, along with dry skin and corneal changes, which can lead to ulceration and rapid destruction of the cornea.

Diagnosis

Dietary history and typical ocular lesions suggest vitamin A deficiency. Carotene levels less than 40 mcg/dl also suggest vitamin A deficiency, but they vary with seasonal ingestion of fruits and vegetables.

CONFIRMING DIAGNOSIS

A serum level of vitamin A that falls below 10 mcg/dl confirms the diagnosis. Levels between 10 and 19 mcg/dl are

also considered low but the patient isn't likely to have developed significant symptoms.

RECOMMENDED DAILY ALLOWANCE OF B-COMPLEX VITAMINS

Vitamin	Men (23 to 50)	Women (23 to 50)	Infants	Children (1 to 10)
B_1*	1.4 mg	1 mg	0.4 mg	0.7 to 1.2 mg
B_2*	1.6 mg	1.2 mg	0.5 mg	0.8 to 1.4 mg
Niacin*	18 mg	13 mg	5 to 8 mg	9 to 16 mg
B_6	2.2 mg	2 mg	0.4 mg	0.9 to 1.6 mg
B_{12}	3 mcg	3 mcg	0.3 mcg	2 to 3 mcg

* requirements per 1,000 kilocalories of dietary intake

Treatment

Mild conjunctival changes or night blindness requires vitamin A replacement in the form of cod liver oil or halibut liver oil. Acute deficiency requires aqueous vitamin A solution I.M., especially when corneal changes have occurred. Therapy for underlying biliary obstruction consists of administration of bile salts; for pancreatic insufficiency, pancreatin. Dry skin responds well to cream-based or petroleum-based products.

In patients with chronic malabsorption of fat-soluble vitamins, and in those with low dietary intake, prevention of vitamin A deficiency requires aqueous I.V. supplements or an oral water-miscible preparation.

Special considerations

- Administer oral vitamin A supplements with or after meals or parenterally, as indicated. Watch for signs of hypercarotenemia (orange coloration of the skin and eyes) and hypervitaminosis A (rash, hair loss, anorexia, transient hydrocephalus, and vomiting in children; bone pain, hepatosplenomegaly, diplopia, and irritability in adults). If these signs occur, discontinue supplements and notify the physician immediately. (Hypercarotenemia is relatively harmless; hypervitaminosis A may be toxic.)

PREVENTION

Because vitamin A deficiency usually results from dietary insufficiency, provide nutritional counseling. Tell the patient that vitamin A comes from animal sources, such as eggs, meat, milk, cheese, cream, liver, kidney, and cod and halibut fish oil, but that healthier choices, such as carrots, pumpkins, sweet potatoes, and most dark green, leafy vegetables are good sources of beta-carotene, vitamin A's precursor form. Instruct the patient that the more intense the color of a fruit or vegetable,

the higher its beta-carotene content. Provide referrals to appropriate community agencies if necessary.

Vitamin B deficiencies

Vitamin B complex is a group of water-soluble vitamins essential to normal metabolism, cell growth, and blood formation. (See *Recommended daily allowance of B-complex vitamins.*) The most common deficiencies involve thiamine (B_1), riboflavin (B_2), niacin, pyridoxine (B_6), and cobalamin (B_{12}).

Causes and incidence

Thiamine deficiency results from malabsorption or inadequate dietary intake of vitamin B_1. It also results from alcoholism, prolonged diarrhea, or from increased requirement, which can occur in pregnancy, lactation, and hyperthyroidism. Beriberi, a serious thiamine-deficiency disease, is most prevalent in Asians, who subsist mainly on diets of unenriched rice and wheat. Although this disease is uncommon in the United States, alcoholics may develop cardiac (wet) beriberi with high-output heart failure, neuropathy, and cerebral disturbances. In times of stress (pregnancy, for example), malnourished young adults may develop beriberi; infantile beriberi may appear in infants on low-protein diets or in those breast-fed by thiamine-deficient mothers.

Riboflavin deficiency (ariboflavinosis) results from a diet deficient in milk, meat, fish, legumes, and green, leafy vegetables. Alcoholism or prolonged diarrhea may also induce riboflavin deficiency. Exposure of milk to sunlight or treatment of legumes with baking soda can destroy riboflavin.

Niacin deficiency, in its advanced form, produces pellagra, which affects the skin, central nervous system (CNS), and GI tract. (See *Recognizing pellagra.*) Although this deficiency is now seldom found in the United States, it was once common among Southerners who subsisted mainly on corn and consumed minimal animal protein. (Corn is low in niacin and in available tryptophan, the amino acid from which the body synthesizes niacin.) Niacin deficiency is still common in parts of Egypt, Romania,

Africa, Serbia, and Montenegro, where corn is the dominant staple food. Niacin deficiency can also occur secondary to carcinoid syndrome or Hartnup disease.

Pyridoxine deficiency usually results from destruction of pyridoxine in infant formulas by autoclaving. A frank deficiency is uncommon in adults, except in patients taking pyridoxine antagonists, such as isoniazid and penicillamine.

Cobalamin deficiency most commonly results from an absence of intrinsic factor in gastric secretions, or an absence of receptor sites after ileal resection. Other causes include malabsorption syndromes associated with sprue, intestinal worm infestation, regional ileitis, and gluten enteropathy, and a diet low in animal protein.

RECOGNIZING PELLAGRA

This patient with pellagra shows dark, scaly, advanced dermatitis. In advanced niacin deficiency, such dermatitis usually occurs on areas exposed to the sun.

Signs and symptoms

Thiamine deficiency causes polyneuritis and, possibly, Wernicke's encephalopathy and Korsakoff's psychosis. In infants (infantile beriberi), this deficiency produces edema, irritability, abdominal pain, pallor, vomiting, loss of voice and, possibly, seizures. In wet beriberi, severe edema starts in the legs and moves up through the body; dry beriberi causes multiple neurologic symptoms and an emaciated appearance. Thiamine deficiency may also cause cardiomegaly, palpitations, tachycardia, dyspnea, and circulatory collapse. Constipation and indigestion are common; ataxia, nystagmus, and ophthalmoplegia are also possible.

Riboflavin deficiency characteristically causes cheilosis (cracking of the lips and corners of the mouth), sore throat, and glossitis. It may also cause seborrheic dermatitis in the nasolabial folds, scrotum, and vulva and, possibly, generalized dermatitis involving the arms, legs, and trunk.

This deficiency can also affect the eyes, producing burning, itching, light sensitivity, tearing, and vascularization of the corneas. Late-stage riboflavin deficiency causes neuropathy, mild anemia and, in children, growth retardation.

Niacin deficiency in its early stages produces fatigue, anorexia, muscle weakness, headache, indigestion, mild skin eruptions, weight loss, and backache. In advanced stages (pellagra), it produces dark, scaly dermatitis, especially on exposed body parts, that makes the patient appear to be severely sunburned. The mouth, tongue, and lips become red and sore, which may interfere with eating. Common GI symptoms include nausea, vomiting, and diarrhea. Associated CNS aberrations—confusion, disorientation, and neuritis—may become severe enough to induce hallucinations and paranoia. Because of this triad of symptoms, pellagra is sometimes called a “3-D” syndrome—dementia, dermatitis, and diarrhea. If not reversed by therapeutic doses of niacin, pellagra can be fatal.

Pyridoxine deficiency in infants causes a wide range of symptoms: dermatitis, occasional cheilosis or glossitis unresponsive to riboflavin therapy, abdominal pain, vomiting, ataxia, and seizures. This deficiency can also lead to CNS disturbances.

Cobalamin deficiency causes pernicious anemia, which produces anorexia, weight loss, abdominal discomfort, constipation, diarrhea, and

glossitis; peripheral neuropathy; and, possibly, ataxia, spasticity, and hyperreflexia.

Diagnosis

The following values confirm vitamin B deficiency.

- *Thiamine deficiency*—commonly measured as micrograms per deciliter in a 24-hour urine collection. Deficiency levels are age-related: 1 to 3 years, less than 120; 4 to 6 years, less than 85; 7 to 9 years, less than 70; 10 to12 years, less than 60; 13 to 15 years, less than 50; adults, less than 27; pregnant women, less than 23 (second trimester), less than 21 (third trimester).
- *Riboflavin deficiency*—measured as micrograms per gram of creatinine in a 24-hour urine collection. Deficiency levels are age-related: 1 to 3 years, less than 150; 4 to 6 years, less than 100; 7 to 9 years, less than 85; 10 to 15 years, less than 70; adults, less than 27; pregnant women, less than 39 (second trimester); less than 30 (third trimester).
- *Niacin deficiency*—measured by Nmethyl nicotinamide in a 24-hour urine collection as micrograms per gram of creatinine. Deficiency levels are: adults, less than 0.5; first trimester of pregnancy, less than 0.5; second trimester, less than 0.6; third trimester, less than 0.8.
- *Pyridoxine deficiency*—xanthurenic acid more than 50 mg/day in 24-hour urine collection after administration of 10 g of L-tryptophan; decreased levels of serum and red blood cell transaminases; reduced excretion of pyridoxic acid in urine.
- *Cobalamin deficiency*—cobalamin serum levels less than 150 pg/ml. Tests to discover the deficiency's cause include gastric analysis and hemoglobin studies. In addition, the Schilling test measures absorption of radioactive cobalamin with and without intrinsic factor.

Treatment

Diet and supplementary vitamins can correct or prevent vitamin B deficiencies, as follows.

- *Thiamine deficiency*—a high-protein diet, with adequate calorie intake, possibly supplemented by B-complex vitamins for early

symptoms. Thiamine-rich foods include pork, peas, wheat bran, oatmeal, and liver. Alcoholic beriberi may require thiamine supplements or thiamine hydrochloride as part of a B-complex concentrate.

- *Riboflavin deficiency*—supplemental riboflavin in patients with intractable diarrhea or increased need for riboflavin related to growth, pregnancy, lactation, or wound healing. Good sources of riboflavin are meats, enriched flour, milk and dairy products, green, leafy vegetables, eggs, and cereal. Acute riboflavin deficiency requires daily oral doses of riboflavin alone or with other B-complex vitamins. Riboflavin phosphate can also be administered I.V. or I.M.
- *Niacin deficiency*—supplemental B-complex vitamins and dietary enrichment in patients at risk because of marginal diets or alcoholism. Meats, fish, peanuts,

  brewer's yeast, enriched breads, and cereals are rich in niacin; milk and eggs, in tryptophan. Confirmed niacin deficiency requires daily doses of niacinamide orally or I.V.
- *Pyridoxine deficiency*—prophylactic pyridoxine therapy in infants and in children with a seizure disorder; supplemental B-complex vitamins in patients with anorexia, malabsorption, or those taking isoniazid or penicillamine. Some women who take hormonal contraceptives may have to supplement their diets with pyridoxine. Confirmed pyridoxine deficiencies require oral or parenteral pyridoxine. Children with convulsive seizures stemming from metabolic dysfunction may require daily doses of 200 to 600 mg pyridoxine.
- *Cobalamin deficiency*—parenteral cobalamin in patients with reduced gastric secretion of hydrochloric acid, lack of intrinsic factor, some malabsorption syndromes, or ileum resections. Strict vegetarians may have to supplement their diets with oral vitamin B_{12}. Depending on the deficiency's severity, supplementary cyanocobalamin or methylcobalamine is usually given parenterally for 5 to 10 days, followed by monthly or daily vitamin B_{12} supplements.

Special considerations

An accurate dietary history provides a baseline for effective dietary counseling.

- Identify and observe patients who are at risk for vitamin B deficiencies —alcoholics, the elderly, pregnant women, oral hormonal contraceptive users (vitamins B_6 and B_{12}), and people on limited diets.
- Administer prescribed supplements. Make sure patients understand how important it is that they adhere strictly to their prescribed treatment for the rest of their lives. Watch for adverse effects from large doses of niacinamide, such as a flushed sensation or hot flashes, in patients with niacin deficiency. Remember, prolonged intake of niacin can cause hepatic dysfunction. Caution patients with Parkinson's disease receiving pyridoxine that this drug can impair response to levodopa therapy.
- Explain all tests and procedures. Reassure patients that, with treatment, the prognosis is good. Refer patients to appropriate assistance agencies if their diets are inadequate due to adverse socioeconomic conditions.

PREVENTION

- *Encourage the patient to follow a well-balanced diet.*
- *Vitamin B_{12} injections can prevent anemia after surgeries known to cause B_{12} deficiency.*

Vitamin C deficiency

Vitamin C (ascorbic acid) deficiency leads to scurvy or inadequate production of collagen, an extracellular substance that binds the cells of the teeth, bones, and capillaries. It's essential for wound healing and burn recovery. Vitamin C is also an important factor in metabolizing such amino acids as tyrosine and phenylalanine. It also acts as a reductant, activating enzymes in the body, as well as converting folic acid into useful components.

Severe vitamin C deficiency results in scurvy, evident by hemorrhagic tendencies and abnormal osteoid and dentin formation.

Causes and incidence

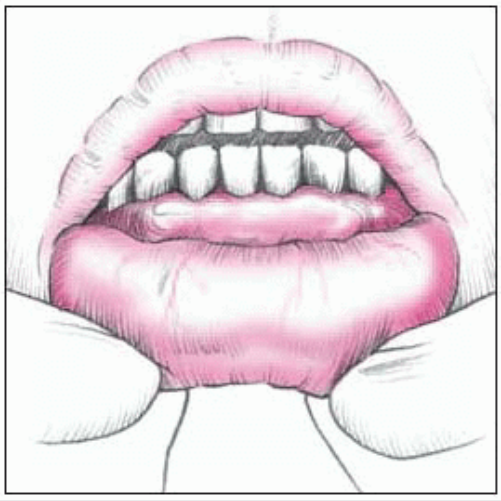
This deficiency's primary cause is a diet lacking in vitamin C-rich foods, such as citrus fruits, tomatoes, cabbage, broccoli, spinach, and berries. Because the body can't store this water-soluble vitamin in large amounts, the supply needs to be replenished daily. Other causes include:

- destruction of vitamin C in foods by overexposure to air or by overcooking
- excessive ingestion of vitamin C during pregnancy, which causes the neonate to require large amounts of the vitamin after birth
- marginal intake of vitamin C during periods of physiologic stress—caused by infectious disease, for example—which can deplete tissue saturation of vitamin C.

Historically common among sailors and others deprived of fresh fruits and vegetables for long periods of time, vitamin C deficiency is uncommon today in the United States, except in alcoholics, people on restricted-residue diets, and infants weaned from breast milk to cow's milk without a vitamin C supplement.

SCURVY'S EFFECT ON GUMS AND LEGS

In adults, scurvy causes swollen or bleeding gums and loose teeth.



It also causes follicular hyperkeratosis, usually on the legs.

Complication

- Scurvy

Signs and symptoms

Clinical features of vitamin C deficiency appear as capillaries become increasingly fragile. In an adult, it produces petechiae, ecchymoses, follicular hyperkeratosis (especially on the buttocks and legs), anemia, anorexia, limb and joint pain (especially in the knees), pallor, weakness, swollen or bleeding gums, loose teeth, lethargy, insomnia, poor wound healing, and ocular hemorrhages in the bulbar conjunctivae. (See *Scurvy's effect on gums and legs*.) Vitamin C deficiency can also cause beading, fractures of the costochondral junctions of the ribs or epiphysis, and such psychological disturbances as irritability, depression, hysteria, and hypochondriasis.

In a child, vitamin C deficiency produces tender, painful swelling in the legs, causing the child to lie with his legs partially flexed. Other

symptoms include fever, diarrhea, and vomiting.

Diagnosis

CONFIRMING DIAGNOSIS

Serum ascorbic acid levels less than 0.2 mg/ dl and white blood cell ascorbic acid levels less than 30 mg/dl help confirm the diagnosis.

Dietary history revealing an inadequate intake of ascorbic acid suggests vitamin C deficiency. A capillary fragility test may be performed on the patient's forearm with a blood pressure cuff; it's positive if more than 10 petechiae form after 5 minutes of pressure.

Treatment

Because scurvy may be fatal, treatment begins immediately to restore adequate vitamin C intake with daily doses of 100 to 200 mg synthetic vitamin C or orange juice in mild disease and with doses as high as 500 mg/day in severe disease. Symptoms usually subside in 2 to 3 days; hemorrhages and bone disorders, in 2 to 3 weeks.

Special considerations

- Administer ascorbic acid orally or by slow I.V. infusion, as indicated. Avoid moving the patient unnecessarily to avoid irritating painful joints and muscles. Encourage him to drink orange juice.
- Explain the importance of supplemental ascorbic acid. Counsel the patient and his family about good dietary sources of vitamin C.
- Advise against taking too much vitamin C. Explain that excessive doses of ascorbic acid may cause nausea, diarrhea, and renal calculi formation and may also interfere with anticoagulant therapy.

PREVENTION

Patients unable or unwilling to consume foods rich in vitamin C or those facing surgery should take daily supplements of ascorbic acid. The recommended daily

allowance is 60 mg/day. Vitamin C supplementation may also prevent this deficiency in recently weaned infants or those drinking formula not fortified with vitamin C.

Vitamin D deficiency

Vitamin D deficiency, commonly called *rickets*, causes failure of normal bone calcification, which occurs through several mechanisms: decreased calcium and phosphorus (the major components of bone) from the intestines, increased excretion of calcium from renal tubules, and increased parathyroid secretion resulting in increased release of calcium from the bone. The deficiency results in rickets in infants and young children and osteomalacia in adults. With treatment, the prognosis is good. However, in rickets, bone deformities usually persist, while in osteomalacia, such deformities may disappear.

Causes and incidence

Vitamin D deficiency results from inadequate dietary intake of preformed vitamin D, malabsorption of vitamin D, or too little exposure to sunlight.

Once a common childhood disease, rickets is now rare in the United States but occasionally appears in breast-fed infants who don't receive a vitamin D supplement or in infants receiving a formula with a nonfortified milk base. This deficiency may also occur in overcrowded urban areas in which smog limits sunlight penetration. Incidence is highest in black children who, because of their skin color, absorb less sunlight. (Solar ultraviolet rays irradiate 7-dehydrocholesterol, a precursor of vitamin D, to form calciferol.)

Osteomalacia, also uncommon in the United States, is most prevalent in Asia, among young multiparas who eat a cereal diet and have minimal exposure to sunlight. Other causes include:

- vitamin D-resistant rickets (refractory rickets, familial hypophosphatemia) from an inherited impairment of renal tubular reabsorption of phosphate (from vitamin D insensitivity)

- conditions that lower absorption of fat-soluble vitamin D, such as chronic pancreatitis, celiac disease, Crohn's disease, cystic fibrosis, gastric or small bowel resections, fistulas, colitis, and biliary obstruction
- hepatic or renal disease, which interferes with the formation of hydroxylated calciferol, necessary to initiate the formation of a calcium-binding protein in intestinal absorption sites
- malfunctioning parathyroid gland (decreased secretion of parathyroid hormone), which contributes to calcium deficiency (normally, vitamin D controls calcium and phosphorus absorption through the intestine) and interferes with activation of vitamin D in the kidneys.

Complications

- Chronic skeletal pain
- Skeletal deformities
- Skeletal fractures

Signs and symptoms

Early indications of vitamin D deficiency are profuse sweating, restlessness, and irritability. Chronic deficiency induces numerous bone malformations due to softening of the bones: bowlegs, knock-knees, rachitic rosary (beading of ends of ribs), enlargement of wrists and ankles, pigeon breast, delayed closing of the fontanels, softening of the skull, and bulging of the forehead. (See *Recognizing bowlegs,* page 554.)

Other rachitic features are poorly developed muscles (potbelly) and infantile tetany. Bone deformities may cause difficulty in walking and in climbing stairs, spontaneous multiple fractures, and lower back and leg pain.

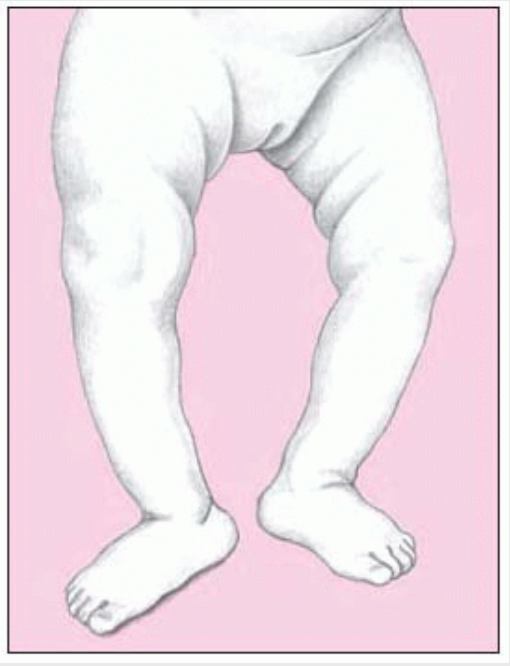
Diagnosis

Physical examination, dietary history, and laboratory tests establish the diagnosis. Test results that suggest vitamin D deficiency include plasma calcium serum levels less than 7.5 mg/dl, serum inorganic phosphorus levels less than 3 mg/dl, serum citrate

levels less than 2.5 mg/dl, and alkaline phosphatase levels less than 4 Bodansky units/dl.

RECOGNIZING BOWLEGS

This infant with rickets shows characteristic bowing of the legs.



CONFIRMING DIAGNOSIS

X-rays confirm the diagnosis by showing characteristic bone deformities and abnormalities such as Looser's zones (pseudofractures).

Treatment

For osteomalacia and rickets—except when caused by malabsorption—treatment consists of oral doses of vitamin D or sources such as fish, liver, and processed milk. Exposure to sunlight is encouraged. For rickets refractory to vitamin D or in rickets accompanied by hepatic or renal disease, treatment includes 25-hydroxycholecalciferol, 1, 25-dihydroxycholecalciferol, or a synthetic analogue of active vitamin D. Replacement of deficient calcium and phosphorus also helps to eliminate

most symptoms of rickets. Positioning or bracing may be used to reduce or prevent deformities; some skeletal deformities may require corrective surgery.

Special considerations

- Obtain a dietary history to assess the patient's current vitamin D intake. Encourage him to eat foods high in vitamin D—fortified milk, fish liver oils, herring, liver, and egg yolks—and get sufficient sun exposure. If deficiency is due to socioeconomic conditions, refer the patient to appropriate community agencies.
- If the patient must take vitamin D for a prolonged period, tell him to watch for signs of vitamin D toxicity (headache, nausea, constipation and, after prolonged use, renal calculi).

PREVENTION

- *Administer supplementary aqueous preparations of vitamin D for chronic fat malabsorption, hydroxylated cholecalciferol for refractory rickets, and supplemental vitamin D for breast-fed infants.*
- *Consider genetic counseling for a patient with a family history of inherited disorders that can cause rickets.*

Vitamin E deficiency

Vitamin E (tocopherol) appears to act primarily as an antioxidant, preventing intracellular oxidation of polyunsaturated fatty acids and other lipids. It protects body tissue from damage caused by unstable substances called free radicals, which can harm cells, tissues, and organs and are believed to be one of the causes of aging's degenerative process. Vitamin E is also important in the formation of red blood cells (RBCs) and helps the body to use vitamin K. Vitamin E deficiency usually manifests as hemolytic anemia in low-birth-weight or premature neonates. With treatment, prognosis is good.

Causes and incidence

Vitamin E deficiency in infants usually results from consuming formulas high in polyunsaturated fatty acids that are fortified with iron but not vitamin E. Such formulas increase the need for antioxidant vitamin E because the iron supplement catalyzes the oxidation of RBC lipids. A neonate has low tissue concentrations of vitamin E to begin with because only a small amount passes through the placenta;

the mother retains most of it. Because vitamin E is a fat-soluble vitamin, deficiency develops in conditions associated with fat malabsorption, such as kwashiorkor, celiac disease, or cystic fibrosis. These conditions may induce megaloblastic or hemolytic anemia and creatinuria, all of which are reversible with vitamin E administration.

Vitamin E deficiency is uncommon in adults but is possible in people whose diets are high in polyunsaturated fatty acids, which increase vitamin E requirements, and in people with vitamin E malabsorption, which impairs RBC survival.

Complication

- Hemolytic anemia

Signs and symptoms

Vitamin E deficiency is difficult to recognize, but its early symptoms include edema and skin lesions in infants and muscle weakness or intermittent claudication in adults. In premature neonates, vitamin E deficiency produces hemolytic anemia, thrombocythemia, and erythematous papular skin eruption, followed by desquamation.

Diagnosis

CONFIRMING DIAGNOSIS

Dietary and medical histories suggest vitamin E deficiency. Serum alphatocopherol levels below 0.5 mg/dl in adults and below 0.2 mg/dl in infants confirm it. Creatinuria, increased creatine kinase levels, hemolytic

anemia, and an elevated platelet count generally support the diagnosis.

Treatment

Replacement of vitamin E with a water-soluble supplement, either oral or parenteral, is the only appropriate treatment.

Special considerations

- As indicated, prevent deficiency by providing vitamin E supplements for low-birth-weight neonates receiving formulas not fortified with vitamin E and for adults with vitamin E malabsorption. Many commercial multivitamin supplements are easily absorbed by patients with vitamin E malabsorption.
- If vitamin E deficiency is related to socioeconomic conditions, refer the patient to appropriate community agencies.

PREVENTION

- *Inform new mothers who plan to breast-feed that human milk provides adequate vitamin E.*
- *Encourage adult patients to eat foods high in vitamin E; good sources include vegetable oils (corn, safflower, soybean, cottonseed); whole grains; dark green, leafy vegetables; nuts; and legumes. Tell them that heavy consumption of polyunsaturated fatty acids increases the need for vitamin E.*

Vitamin K deficiency

Deficiency of vitamin K, an element necessary for formation of prothrombin and other clotting factors in the liver, produces abnormal bleeding. If the deficiency is corrected, the prognosis is excellent.

Causes and incidence

Vitamin K deficiency is common among neonates in the first few days postpartum due to poor placental transfer of vitamin K and inadequate production of vitamin Kproducing intestinal flora. Its other causes include prolonged use of drugs, such as the anticoagulant warfarin and antibiotics that destroy normal intestinal bacteria; decreased flow of bile to the small intestine from obstruction of the bile duct or bile fistula; malabsorption of vitamin K due to sprue, pellagra, bowel resection, ileitis, or ulcerative colitis; chronic hepatic disease, with impaired response of hepatic ribosomes to vitamin K; and cystic fibrosis, with fat malabsorption. Vitamin K deficiency seldom results from insufficient dietary intake of this vitamin.

Signs and symptoms

The cardinal sign of vitamin K deficiency is an abnormal bleeding tendency, accompanied by prolonged prothrombin time (PT); these signs disappear with vitamin K administration. Without treatment, bleeding may be severe and, possibly, fatal.

Diagnosis

CONFIRMING DIAGNOSIS

A PT that's 25% longer than the normal range of 10 to 20 seconds, measured by the Quick method, confirms the diagnosis of vitamin K deficiency after other causes of prolonged PT (such as anticoagulant therapy or hepatic disease) have been ruled out. The international normalized ratio (normal value, 0.8 to 1.2) is the more common method of assessing PT adequacy.

Repetition of testing in 24 hours (and regularly during treatment) monitors the therapy's effectiveness.

Treatment

Administration of vitamin K I.V. or I.M. corrects abnormal bleeding tendencies.

Special considerations

PREVENTION

- *Administer vitamin K to neonates and patients with fat malabsorption or with prolonged diarrhea from colitis, ileitis, or long-term antibiotic drug therapy.*
- *If the deficiency has a dietary cause, help the patient and his family plan a diet that includes important sources of vitamin K, such as cauliflower, tomatoes, cheese, egg yolks, liver, and green, leafy vegetables.*
- Warn against self-medication with or overuse of antibiotics, because these drugs destroy the intestinal bacteria needed to generate significant amounts of vitamin K.

Hypervitaminoses A and D

Hypervitaminosis A is excessive accumulation of vitamin A; hypervitaminosis D, of vitamin D. Although these are toxic conditions, they usually respond well to treatment. They're most prevalent in infants and children, usually as a result of accidental or misguided overdosage by parents. A related, benign condition called hypercarotenemia results from excessive consumption of carotene, a chemical precursor of vitamin A.

Causes and incidence

Vitamins A and D are fat-soluble vitamins that accumulate in the body because they aren't dissolved and excreted in the urine. (See *Important facts about vitamins A and D*.) In most cases, hypervitaminoses A and D result from ingestion of excessive amounts of supplemental vitamin preparations. A single dose of more than 1 million units of vitamin A can cause acute toxicity; daily doses of 15,000 to 25,000 units taken over weeks or months have proven toxic in infants and children. For the same dose to produce toxicity in adults, ingestion over years is necessary. Doses of 100,000 international units of vitamin D daily for several

months can cause toxicity in adults. Individuals who are at risk include those with hyperparathyroidism, kidney disease, sarcoidosis, tuberculosis, or histoplasmosis.

PEDIATRIC TIP

In infants, giving 40,000 international units daily of vitamin D can cause toxicity in 1 to 4 months.

Hypervitaminosis A may occur in patients receiving pharmacologic doses of vitamin A for dermatologic disorders. Hypervitaminosis D may occur in patients receiving high doses of the vitamin as treatment for hypoparathyroidism, rickets, and the osteodystrophy of chronic renal failure, and in infants who consume fortified milk and cereals plus a vitamin supplement. Concentrations of vitamin A in common foods are generally too low to pose a danger of excessive intake. However, a benign condition called *hypercarotenemia* results from excessive consumption of vegetables high in carotene (a protovitamin that the body converts into vitamin A), such as carrots, sweet potatoes, and dark green, leafy vegetables.

Signs and symptoms

Chronic hypervitaminosis A produces anorexia, irritability, headache, hair loss, malaise, itching, vertigo, bone pain, bone fragility, and dry, peeling skin. It may also cause hepatosplenomegaly and emotional lability. Acute toxicity may also produce transient hydrocephalus and vomiting. (Hypercarotenemia produces yellow or orange skin coloration.)

Hypervitaminosis D causes anorexia, headache, nausea, vomiting, weight loss, polyuria, and polydipsia. Because vitamin D promotes calcium absorption, severe toxicity can lead to hypercalcemia, including calcification of soft tissues, as in the

heart, aorta, and renal tubules. Lethargy, confusion, and coma may accompany severe hypercalcemia.

IMPORTANT FACTS ABOUT VITAMINS A AND D

This table illustrates good sources of vitamins A and D, their recommended daily allowances, and the actions

they produce.

Vitamin	Sources	Recommended dietary allowance	Action
Vitamin A	▪ Carrots; sweet potatoes; dark green, leafy vegetables; butter; margarine; liver; egg yolk	▪ Children: 1,400 international units ▪ Adults: 4,000 to 5,000 international units ▪ Lactating women: 6,000 international units	▪ Produces retinal pigment and maintains epithelial tissue
Vitamin D	▪ Ultraviolet light; fortified foods (especially milk)	▪ 400 international units daily	▪ Promotes absorption and regulates metabolism of calcium and phosphorus

Diagnosis

A thorough patient history suggests hypervitaminosis A.

CONFIRMING DIAGNOSIS

An elevated serum vitamin A level (over 90 mcg/dl) confirms hypervitaminosis A.

Patient history and an elevated serum calcium level (over 10.5 mcg/dl) suggest hypervitaminosis D.

CONFIRMING DIAGNOSIS

An elevated serum vitamin D level confirms hypervitaminosis D.

In children, X-rays showing calcification of tendons, ligaments, and subperiosteal tissues support this diagnosis.

CONFIRMING DIAGNOSIS

An elevated serum carotene level (over 250 mcg/dl) confirms hypercarotenemia.

Treatment

Withholding vitamin supplements usually corrects hypervitaminosis A quickly and hypervitaminosis D gradually. Hypercalcemia may persist for weeks or months after the patient stops taking vitamin D. Treatment for severe hypervitaminosis D may include glucocorticoids to control hypercalcemia and prevent renal damage. In the acute stage, diuretics or other emergency measures for severe hypercalcemia may be necessary. Hypercarotenemia responds well to a diet free of high-carotene foods.

Special considerations

- Keep the patient comfortable, and reassure him that symptoms will subside after he stops taking the vitamin.
- Make sure the patient or the parents of a child with these conditions understand that vitamins aren't innocuous. Explain the hazards associated with excessive vitamin intake. Point out that vitamin A and D requirements can easily be met with a diet containing dark green, leafy vegetables; fruits; and fortified milk or milk products.

PREVENTION

Monitor serum vitamin A levels in patients receiving doses above the recommended daily allowance and serum calcium levels in patients receiving pharmacologic doses of vitamin D.

Iodine deficiency

Iodine deficiency is the absence of sufficient levels of iodine to satisfy daily metabolic requirements. Because the thyroid gland uses most of the body's iodine stores,

iodine deficiency is apt to cause hypothyroidism and thyroid gland hypertrophy (endemic goiter). Other effects of deficiency range from dental caries to cretinism in neonates born to iodine-deficient mothers. Iodine deficiency is most common in pregnant or lactating women due to their exaggerated metabolic need for this element. Iodine deficiency responds readily to treatment with iodine supplements.

Causes and incidence

Iodine deficiency usually results from insufficient intake of dietary sources of iodine, such as iodized table salt, seafood, and dark green, leafy vegetables. (Normal iodine requirements range from 35 mcg/ day for infants to 150 mcg/day for lactating women; the average adult needs 1 mcg/kg of body weight.) Iodine deficiency may also result from an increase in metabolic demands during pregnancy, lactation, and adolescence.

Complications

- Hypothyroidism
- Goiter

Signs and symptoms

Clinical features of iodine deficiency depend on the degree of hypothyroidism that develops (in addition to the development of a goiter). Mild deficiency may produce only mild, nonspecific symptoms, such as lassitude, fatigue, and loss of motivation. Severe deficiency usually generates the typically overt and unmistakable features of hypothyroidism: bradycardia; decreased pulse pressure and cardiac output; weakness; hoarseness; dry, flaky, inelastic skin; puffy face; thick tongue; delayed relaxation phase in deep tendon reflexes; poor memory; hearing loss; chills; anorexia; and nystagmus. In women, iodine deficiency may also cause menorrhagia and amenorrhea.

Cretinism—hypothyroidism that develops in utero or in early infancy—is characterized by failure to thrive, neonatal jaundice, and hypothermia.

By age 3 to 6 months, the infant may display spastic diplegia and signs and symptoms similar to those seen in infants with Down syndrome.

Diagnosis

CONFIRMING DIAGNOSIS

Abnormal laboratory test results include low thyroxine (T_4) levels with high radioactive iodine (^{131}I) uptake, low 24-hour urine iodine levels, and high thyroid-stimulating hormone levels. Radioiodine uptake test traces ^{131}I in the thyroid 24 hours after administration; triiodothyronine-resin or T_4-resin uptake test shows values 25% below normal.

Treatment

Severe iodine deficiency requires administration of iodine supplements (potassium iodide [SSKI]). Mild deficiency may be corrected by increasing iodine intake through the use of iodized table salt and consumption of iodine-rich foods (seafood and green, leafy vegetables).

Special considerations

- Administer SSKI preparation in milk or juice to reduce gastric irritation and mask its metallic taste. To prevent tooth discoloration, tell the patient to drink the solution through a straw. Store the solution in a light-resistant container.

PREVENTION

- *Recommend the use of iodized salt and consumption of iodine-rich foods for high-risk patients—especially adolescents and pregnant or lactating women.*
- *Advise pregnant women that severe iodine deficiency may produce cretinism in neonates, and instruct them to watch for early signs of iodine deficiency, such as*

fatigue, lassitude, weakness, and decreased mental function.

Zinc deficiency

Zinc, an essential trace element that's present in the bones, teeth, hair, skin, testes, liver, and muscles, is also a vital component of many enzymes. Zinc promotes synthesis of deoxyribonucleic acid, ribonucleic acid and, ultimately, protein, and maintains normal blood concentrations of vitamin A by mobilizing it from the liver. The prognosis is good with correction of the deficiency.

Causes and incidence

Zinc deficiency usually results from excessive intake of foods (containing iron, calcium, vitamin D, and the fiber and phytates in cereals) that bind zinc to form insoluble chelates that prevent its absorption. Occasionally, it results from blood loss due to parasitism and low intake of foods containing zinc. Alcohol and corticosteroids increase renal excretion of zinc.

Zinc deficiency is most common in people from underdeveloped countries, especially in the Middle East. Children are most susceptible to this deficiency during periods of rapid growth.

Signs and symptoms

Zinc deficiency produces hepatosplenomegaly, sparse hair growth, soft and misshapen nails, poor wound healing, anorexia, hypogeusesthesia (decreased taste acuity), dysgeusia (unpleasant taste), hyposmia (decreased odor acuity), dysosmia (unpleasant odor in nasopharynx), severe iron deficiency anemia, bone deformities and, when chronic, hypogonadism, dwarfism, and hyperpigmentation.

Diagnosis

CONFIRMING DIAGNOSIS

Fasting serum zinc levels below 70 mcg/ dl confirm zinc deficiency and indicate altered phosphate metabolism, imbalance between aerobic and anaerobic metabolism, and decreased pancreatic enzyme levels.

Treatment

Treatment consists of correcting the deficiency's underlying cause and administering zinc supplements, as necessary.

Special considerations

- Advise the patient to take zinc supplements with milk or meals to prevent gastric distress and vomiting.

PREVENTION

Encourage a balanced diet that includes seafood, oatmeal, bran, meat, eggs, nuts, and dry yeast and the correct use of calcium and iron supplements.

Obesity

Obesity is an excess of body fat, generally 20% above ideal body weight. The prognosis for correction of obesity is poor: Fewer than 30% of patients succeed in losing 20 lb (9 kg), and only half of these maintain the loss over a prolonged period.

Causes and incidence

Obesity results from excessive calorie intake and inadequate expenditure of energy. Theories to explain this condition include hypothalamic dysfunction of hunger and satiety centers, genetic predisposition, abnormal absorption of nutrients, and impaired action of GI and growth hormones and of hormonal regulators such as insulin. An inverse relationship between socioeconomic status and the prevalence of obesity has been documented, especially in women. Obesity in parents increases the probability of obesity in children, from genetic or environmental factors, such as activity levels and learned patterns of

eating. Psychological factors, such as stress or emotional eating, may also contribute to obesity. Rates of obesity are climbing, and the percentage of children and adolescents who are obese has doubled in the last 20 years.

Complications

- Respiratory difficulties
- Hypertension
- Cardiovascular disease
- Diabetes mellitus
- Renal disease
- Gallbladder disease
- Psychosocial difficulties
- Premature death

Diagnosis

Observation and comparison of height and weight to a standard table indicate obesity. Measurement of the thickness of subcutaneous fat folds with calipers provides an approximation of total body fat. Although this measurement is reliable and isn't subject to daily fluctuations, it has little meaning for the patient in monitoring subsequent weight loss.

Treatment

Successful management of obesity must decrease the patient's daily calorie intake while increasing his activity level. Effective treatment must be based on a balanced, low-calorie diet that eliminates foods high in fat or sugar. Lifelong maintenance of these improved eating and exercise patterns is necessary to achieve long-term benefits.

The popular low-carbohydrate diets offer no long-term advantage; rapid early weight reduction is due to loss of water, not fat. These and other crash or fad diets have the overwhelming drawback that they don't teach the patient long-term modification of eating patterns and often

lead to the “yo-yo syndrome”—episodes of repeated weight loss followed by weight gain. This can be more detrimental than the obesity itself because of the severe stress it can place on the body.

Total fasting is an effective method of rapid weight reduction but requires close monitoring and supervision to minimize risks of ketonemia, electrolyte imbalance, hypotension, and loss of lean body mass. Prolonged fasting and very-low-calorie diets have been associated with sudden death, possibly resulting from cardiac arrhythmias caused by electrolyte abnormalities. These methods also neglect patient re-education, which is necessary for long-term weight maintenance.

Treatment may also include hypnosis and behavior modification techniques, which promote fundamental changes in eating habits and activity patterns. In addition, psychotherapy may be beneficial for some patients, because weight reduction may lead to depression or even psychosis. Antidepressants are also helpful in weight loss.

Amphetamines and amphetamine congeners have been used to enhance compliance with a prescribed diet by temporarily suppressing the appetite and creating a feeling of well-being. However, because their value in long-term weight control is questionable, and they have significant potential for dependence and abuse, their use is generally avoided. If these drugs are used at all, they should be prescribed only for short-term therapy and should be monitored carefully.

As a last resort, morbid obesity, which is indicated by body weight that's 50% to 100% higher than ideal, body weight that's 100 pounds higher than ideal, or a body mass index greater than 39, may be treated surgically with a variety of restrictive procedures. The two most popular bariatric surgeries are vertical banded gastroplasty and gastric bypass surgery. These procedures decrease the volume of food that the stomach can hold or bypass the stomach, with the goal of producing satiety with small intake. Bypassing the stomach also induces diarrhea when concentrated sweets are ingested. These techniques cause fewer complications than jejunoileal bypass, which induces a permanent malabsorption syndrome. Extended liquid diets are necessary adjuncts to surgery. Psychological counseling is also recommended.

Special considerations

- Obtain an accurate diet history to identify the patient's eating patterns and the importance of food to his lifestyle. Ask the patient to keep a careful record of what, where, and when he eats to help identify situations that normally provoke overeating.
- Explain the prescribed diet carefully, and encourage compliance to improve health status.
- To increase calorie expenditure, promote increased physical activity, including an exercise program. Recommend varying activity levels according to the patient's general condition and cardiovascular status.
- Watch carefully for signs of dependence or abuse if the patient is taking appetitesuppressing drugs; also watch for adverse effects, such as insomnia, excitability, dry mouth, and GI disturbances.
- Teach the grossly obese patient the importance of good skin care to prevent breakdown in moist skin folds. Recommend the regular use of powder to keep skin dry.
- The patient having gastric bypass surgery should receive psychological and nutritional counseling before and after the surgery to assist with dietary and lifestyle changes.

PREVENTION

- *Teach parents to avoid overfeeding their infants and to familiarize themselves with actual nutritional needs and optimum growth rates. Discourage parents from using food to reward or console their children, from emphasizing the importance of "clean plates," and from allowing eating to prevent hunger rather than to satisfy it.*
- *Encourage physical activity and exercise, especially in children and young adults, to establish lifelong patterns. Suggest low-calorie snacks such as raw vegetables.*

Protein-calorie malnutrition

One of the most prevalent and serious depletion disorders, protein-calorie malnutrition (PCM) occurs as marasmus (protein-calorie deficiency), characterized by growth failure and wasting, and as kwashiorkor (protein deficiency), characterized by tissue edema and damage. Both forms vary from mild to severe and may be fatal, depending on the accompanying stress (particularly sepsis or injury) and duration of deprivation. PCM increases the risk of death from pneumonia, chickenpox, or measles.

Causes and incidence

Both kwashiorkor (edematous PCM) and marasmus (nonedematous PCM) are common in underdeveloped countries and in areas in which dietary amino acid content is insufficient to satisfy growth requirements. Kwashiorkor typically occurs at about age 1, after infants are weaned from breast milk to a protein-deficient diet of starchy gruels or sugar water, but it can develop at any time during the formative years. Marasmus affects infants ages 6 to 18 months as a result of breast-feeding failure, or a debilitating condition such as chronic diarrhea.

In industrialized countries, PCM may occur secondary to chronic metabolic disease that decreases protein and calorie intake or absorption, or trauma that increases protein and calorie requirements.

ELDER TIP

In the United States, PCM is estimated to occur to some extent in 50% of elderly people in nursing homes.

Those who aren't allowed anything by mouth for an extended period are at high risk of developing PCM. Conditions that increase protein-calorie requirements include severe burns and injuries, systemic infections, and cancer (accounts for the largest group of hospitalized patients with PCM). Conditions that cause defective utilization of nutrients include malabsorption syndrome, short-bowel syndrome, and Crohn's disease.

Signs and symptoms

Children with chronic PCM are small for their chronological age and tend to be physically inactive, mentally apathetic, and susceptible to frequent infections. Anorexia and diarrhea are common.

In acute PCM, children are small, gaunt, and emaciated, with no adipose tissue. Skin is dry and “baggy,” and hair is sparse and dull brown or reddish-yellow. Temperature is low; pulse rate and respirations are slowed. Such children are weak, irritable, and usually hungry, although they may have anorexia, with nausea and vomiting.

Unlike marasmus, chronic kwashiorkor allows the patient to grow in height, but adipose tissue diminishes as fat metabolizes to meet energy demands. Edema often masks severe muscle wasting; dry, peeling skin and hepatomegaly are common. Patients with secondary PCM show signs similar to marasmus, primarily loss of adipose tissue and lean body mass, lethargy, and edema. Severe secondary PCM may cause loss of immunocompetence.

Diagnosis

CONFIRMING DIAGNOSIS

Clinical appearance, dietary history, and anthropometry confirm PCM. If the patient doesn't suffer from fluid retention, weight change over time is the best index of nutritional status.

The following factors support the diagnosis:

- height and weight less than 80% of standard for the patient's age and sex, and

  below-normal arm circumference and triceps skinfold
- serum albumin level less than 2.8 g/dl (normal: 3.3 to 4.3 g/dl)
- urinary creatinine (24-hour) level used to show lean body mass status by relating creatinine excretion to height and ideal body weight, to yield creatinine-height index.

Treatment

The aim of treatment is to provide sufficient proteins, calories, and other nutrients for nutritional rehabilitation and maintenance. When treating severe PCM, restoring fluid and electrolyte balance parentally is

the initial concern. A patient who shows normal absorption may receive enteral nutrition after anorexia has subsided. When possible, the preferred treatment is oral feeding. Foods are introduced slowly. Carbohydrates are given first to supply energy, and then high-quality protein foods, especially milk, and protein-calorie supplements, are given. A patient who's unwilling or unable to eat may require supplementary feedings through a nasogastric tube or total parenteral nutrition (TPN), which is given through a central venous catheter because of its higher osmolality. Peripheral parenteral nutrition, which has a lower osmolality than TPN and can be given through a peripheral I.V. line, is an alternative to TPN, but it's given less commonly. Accompanying infection must also be treated, preferably with antibiotics that don't inhibit protein synthesis. Cautious realimentation is essential to prevent complications from overloading the compromised metabolic system.

Special considerations

- Encourage the patient with PCM to consume as much nutritious food and beverage as possible. (It's often helpful to “cheer him on” as he eats.) Assist the patient with eating if necessary. Cooperate closely with the dietitian to monitor intake, and provide acceptable meals and snacks.
- If TPN is necessary, observe strict sterile technique when handling catheters, tubes, and solutions and during dressing changes.

PREVENTION

- *Watch for PCM in patients who have been hospitalized for a prolonged period, have had no oral intake for several days, or have cachectic disease.*
- *To help eradicate PCM in developing countries, encourage prolonged breast-feeding, educate mothers about their children's needs, and provide supplementary foods, as needed.*

ELDER TIP

If the older patient is anorectic, consider asking family members and other visitors to bring in special foods from home that may improve the patient's appetite. In addition, encouraging the family to collaborate on feeding a dependent patient can help promote his recovery, enhance his feelings of well-being, and stimulate him to eat more.

METABOLIC DISORDERS

Galactosemia

Galactosemia is any disorder of galactose metabolism. It produces symptoms ranging from cataracts and liver damage to mental retardation and occurs in two forms: classic galactosemia and galactokinase-deficiency galactosemia. Although a galactose-free diet relieves most symptoms, galactosemia-induced mental impairment is irreversible; some residual vision impairment may also persist.

Causes and incidence

Both forms of galactosemia are inherited as autosomal recessive defects and occur in about 1 in 60,000 births in the United States. Up to 1.25% of the population is heterozygous for the classic galactosemia gene. Classic galactosemia results from a defect in the enzyme galactose-1-phosphate uridyl transferase. (See *Metabolic pathway in galactosemia*.) Galactokinasedeficiency galactosemia, the rarer form of this disorder, stems from a deficiency of the enzyme galactokinase. In both forms of galactosemia, the inability to normally metabolize the sugar galactose (which is

mainly formed by digestion of the disaccharide lactose that's present in milk) causes galactose accumulation.

Complications

- Ovarian dysfunction

- Cataracts
- Abnormal speech
- Cognitive impairment
- Motor delay
- Growth retardation

Signs and symptoms

In children who are homozygous for the classic galactosemia gene, signs are evident at birth or begin within a few days after milk ingestion, and include failure to thrive, vomiting, and diarrhea. Other clinical effects include liver damage (which causes jaundice, hepatomegaly, cirrhosis, and ascites), splenomegaly, galactosuria, proteinuria, and aminoaciduria. Cataracts may also be present at birth or develop later. Pseudotumor cerebri may occur.

Continued ingestion of galactose- or lactose-containing foods may cause mental retardation, malnourishment, progressive hepatic failure, and death—from the stillunknown process of galactose metabolites accumulating in body tissues. Although treatment may prevent mental impairment, galactosemia can produce a short attention span, difficulty with spatial and mathematical relationships, and apathetic, withdrawn behavior. Cataracts may be the only sign of galactokinase deficiency, resulting from the accumulation of galactitol, a metabolic by-product of galactose, in the lens.

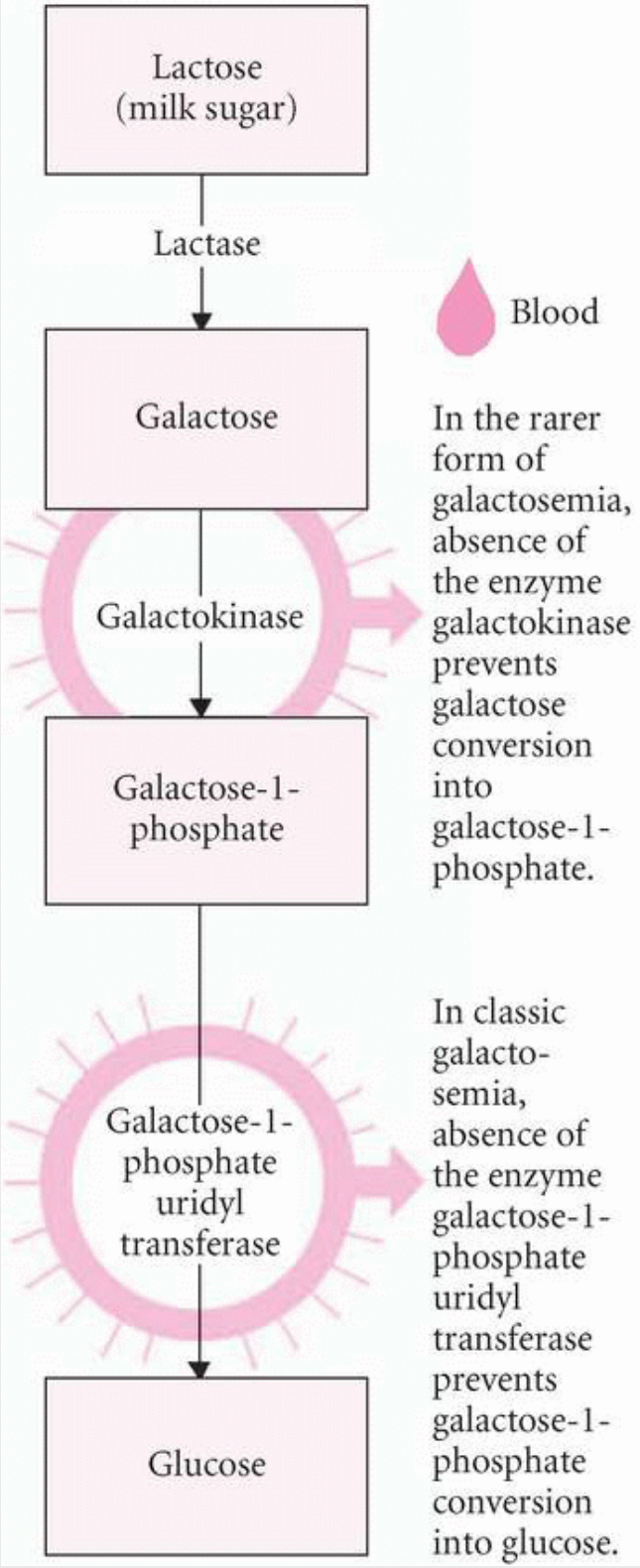
Diagnosis

CONFIRMING DIAGNOSIS

Deficiency of the enzyme galactose-1-phosphate uridyl transferase in red blood cells (RBCs) confirms classic galactosemia; decreased RBC levels of galactokinase confirm galactokinase deficiency. Prenatal diagnosis may be made by direct measurement of galactose-1-phosphate uridyl transferase.

Related laboratory results include increased galactose levels in blood (normal value in children is less than 20 mg/dl) and urine (must use galactose oxidase to avoid confusion with other reducing sugars). Galactose measurements in blood and urine must be interpreted carefully because some children who consume large amounts of milk have elevated plasma galactose concentrations and galactosuria but aren't galactosemic. Also, neonates excrete galactose in their urine for about a week after birth; premature infants, even longer.

METABOLIC PATHWAY IN GALACTOSEMIA



Other test results include:

DIET FOR GALACTOSEMIA

A patient with galactosemia must follow a lactose-free diet. It's important for him to carefully read food labels to avoid milk and milk products, including dry milk products. He may eat these foods:

- fish and animal products (except brains and mussels)
- fresh fruits and vegetables (except peas and lima beans)
- only bread and rolls made from cracked wheat.

He should avoid these foods:

- dairy products
- puddings, cookies, cakes, pies
- food coloring
- instant potatoes
- canned and frozen foods (if lactose is listed as an ingredient).

- liver biopsy—typical acinar formation
- liver enzymes (aspartate aminotransferase, alanine aminotransferase levels)—elevated
- urinalysis—albumin in urine
- ophthalmoscopy—punctate lesions in the fetal lens nucleus (with treatment, cataracts regress)
- amniocentesis—prenatal diagnosis of galactosemia (recommended for heterozygous and homozygous parents).

Treatment

Elimination of galactose and lactose from the diet causes most effects to subside. The infant is fed soy formula, meat-base formula, protein hydrolysate formula, or another lactose-free formula. The infant gains

weight; liver anomalies, nausea, vomiting, galactosemia, proteinuria, and aminoaciduria disappear; and cataracts regress. As the child grows, a balanced, galactose-free diet must be maintained. A pregnant woman who's heterozygous or homozygous for galactosemia should also follow a galactose-restricted diet. Such a diet supports normal growth and development and may delay symptoms in the neonate.

Special considerations

- To eliminate galactose and lactose from an infant's diet, replace cow's milk formula or breast milk with a meat-base or soybean formula.
- Teach the parents about dietary restrictions and stress the importance of compliance. (See *Diet for galactosemia*.) Warn them to read medication labels carefully and avoid giving any medication that contains lactose fillers.
- If the child has a learning disability, help parents secure educational assistance. Refer parents who want to have other children for genetic counseling. In some states, screening of all neonates for galactosemia is required by law.
- Instruct the parents to contact support groups, such as Parents of Galactosemic Children, for further information and support if appropriate.

Glycogen storage diseases

Glycogen storage diseases consist of at least eight distinct errors of metabolism, all inherited, that alter the synthesis or degradation of glycogen, the form in which glucose is stored in the body. Normally, muscle and liver cells store glycogen. Muscle glycogen is used in muscle contraction; liver glycogen can be converted into free glucose, which can then diffuse out of the liver cells to increase blood glucose levels. Glycogen storage diseases manifest as dysfunctions of the liver, heart, or musculoskeletal system. Symptoms vary from mild and easily controlled hypoglycemia to severe organ involvement that may lead to heart failure and respiratory failure.

Causes and incidence

Almost all glycogen storage diseases (Types I through V and Type VII) are transmitted as autosomal recessive traits. The transmission mode of Type VI is unknown; Type VIII may be an X-linked trait.

The most common glycogen storage disease is Type I—von Gierke's, or hepatorenal glycogen storage disease—which results from a deficiency of the liver enzyme glucose-6-phosphatase. This enzyme converts glucose-6-phosphate into free glucose

and is necessary for the release of stored glycogen and glucose into the bloodstream, to relieve hypoglycemia. Infants may die of acidosis before age 2; if they survive past this age, with proper treatment, they may grow normally and live to adulthood, with only minimal hepatomegaly. However, there's a danger of adenomatous liver nodules, which may be premalignant.

Complications

- Heat intolerance
- Easy bruising
- Slowed growth
- Incomplete sexual development
- Hepatic ademonas
- Multiple organ failure

Signs and symptoms

Primary clinical features of the liver glycogen storage diseases (Types I, III, IV, VI, and VIII) are hepatomegaly and rapid onset of hypoglycemia and ketosis when food is withheld. Symptoms of the muscle glycogen storage diseases (Types II, V, and VII) include poor muscle tone; Type II may result in death from heart failure. (See *Rare forms of glycogen storage disease,* pages 566 and 567.)

In addition, Type I may produce these symptoms:

- infants—acidosis, hyperlipidemia, GI bleeding, coma

- children—low resistance to infection and, without proper treatment, short stature
- adolescents—gouty arthritis and nephropathy; chronic tophaceous gout; bleeding (especially epistaxis); small superficial vessels visible in skin due to impaired platelet function; fat deposits in cheeks, buttocks, and subcutaneous tissues; poor muscle tone; enlarged kidneys; xanthomas over extensor surfaces of arms and legs; steatorrhea; multiple, bilateral, yellow lesions in fundi; and osteoporosis, probably secondary to negative calcium balance. Correct treatment of glycogen storage disease should prevent all of these effects.

Diagnosis

CONFIRMING DIAGNOSIS

Liver biopsy confirms the diagnosis by showing normal glycogen synthetase and phosphorylase enzyme activities but reduced or absent glucose-6-phosphatase activity. Glycogen structure is normal but amounts are elevated. Spectroscopy may be used to show abnormal muscle metabolism with the use of magnetic resonance imaging in specialized centers.

- Laboratory studies of plasma demonstrate low glucose levels but high levels of free fatty acids, triglycerides, cholesterol, and uric acid. Serum analysis reveals high pyruvic acid levels and high lactic acid levels. Prenatal diagnoses are available for Types II, III, and IV.
- Injection of glucagon or epinephrine increases pyruvic and lactic acid levels but doesn't increase blood glucose levels. Glucose tolerance test curve typically shows depletional hypoglycemia and reduced insulin output. Intrauterine diagnosis is possible.

Treatment

For Type I, treatment aims to maintain glucose homeostasis and prevent secondary consequences of hypoglycemia through frequent feedings and constant nocturnal nasogastric (NG) drip with Polycose, dextrose, or

Vivonex. Treatment includes a low-fat diet, with normal amounts of protein and calories; carbohydrates should contain glucose or glucose polymers only.

Therapy for Type III includes frequent feedings and a high-protein diet. Type IV requires a high-protein, high-calorie diet; bed rest; diuretics; sodium restriction; and paracentesis, if necessary, to relieve ascites. Types V and VII require no treatment except avoidance of strenuous exercise. No treatment is necessary for Types VI and VIII; no effective treatment exists for Type II.

Special considerations

When managing Type I disease:

- Advise the patient or his parents to include carbohydrate foods containing mainly starch in his diet and to sweeten foods with glucose only.
- Before discharge, teach the patient or his family member how to pass an NG tube, use a pump with alarm capacity, monitor blood glucose levels with glucose reagent strips, and recognize symptoms of hypoglycemia.

RARE FORMS OF GLYCOGEN STORAGE DISEASE

Type	Clinical features	Diagnostic test results
II (Pompe's)		
Absence of alpha-1,4-glucosidase (acid maltase)	▪ *Infants:* cardiomegaly, profound hypotonia and, occasionally, endocardial fibroelastosis (usually fatal before age 1 due to cardiac or respiratory failure) ▪ *Some infants and young children:* muscle weakness and wasting, variable organ involvement (slower	▪ *Muscle biopsy:* increased concentration of glycogen with normal structure; alpha-1,4-glucosidase deficiency ▪ *Electrocardiogram (in infants):* large QRS complexes in all leads; inverted T waves; shortened PR interval ▪ *Electromyography (in adults):* muscle fiber

	progression, usually fatal by age 19) ▪ *Adults:* muscle weakness without organomegaly (slowly progressive but not fatal)	irritability; myotonic discharges ▪ *Amniocentesis:* alpha-1,4-glucosidase deficiency ▪ *Placenta or umbilical cord examination:* alpha-1,4-glucosidase deficiency
III (Cori's)		
Absence of debranching enzyme (amylo-1,6-glucosidase) (*Note:* predominant cause of glycogen storage disease in Israel)	▪ *Young children:* massive hepatomegaly, which may disappear by puberty; growth retardation; moderate splenomegaly; hypoglycemia ▪ *Adults:* progressive myopathy ▪ Occasionally, moderate cardiomegaly, cirrhosis, muscle wasting, hypoglycemia	▪ *Liver biopsy:* deficient debranching activity; increased glycogen concentration ▪ *Laboratory tests (in children only):* elevated aspartate aminotransferase or alanine aminotransferase levels; increased erythrocyte glycogen levels
IV (Andersen's)		
Deficiency of branching enzyme (amylo-1,4-1,6-transglucosidase) (*Note:* extremely rare)	▪ *Infants:* hepatosplenomegaly, ascites, muscle hypotonia; usually fatal before age 2 from progressive cirrhosis	▪ *Liver biopsy:* deficient branching enzyme activity; glycogen molecule has longer outer branches
V (McArdle's)		
Deficiency of muscle phosphorylase	▪ *Children:* mild or no symptoms ▪ *Adults:* muscle cramps and pain during strenuous exercise, possibly resulting in myoglobinuria and renal failure ▪ *Older patients:* significant muscle weakness and wasting	▪ *Serum lactate:* no increase in venous levels in sample drawn from extremity after ischemic exercise ▪ *Muscle biopsy:* lack of phosphorylase activity; increased glycogen content
VI (Hers')		

Possible deficiency of hepatic phosphorylase	▪ Mild symptoms (similar to those of Type I), requiring no treatment	▪ *Liver biopsy:* decreased phosphorylase *b* activity, increased glycogen concentration
VII		
Deficiency of muscle phosphofructokinase	▪ Muscle cramps during strenuous exercise, resulting in myoglobinuria and possible renal failure ▪ Reticulocytosis	▪ *Serum lactate:* no increase in venous levels in sample drawn from extremity after ischemic exercise ▪ *Muscle biopsy:* deficient phosphofructokinase; marked rise in glycogen concentration ▪ *Blood studies:* low erythrocyte phosphofructokinase activity; reduced half-life of red blood cells
VIII		
Deficiency of hepatic phosphorylase kinase	▪ Mild hepatomegaly ▪ Mild hypoglycemia	▪ *Liver biopsy:* deficient phosphorylase *b* kinase activity; increased glycogen concentration ▪ *Blood study:* deficient phosphorylase *b* kinase in leukocytes

- Watch for and report signs of infection (fever, chills, myalgia) and of hepatic encephalopathy (mental confusion, stupor, asterixis, coma) due to increased blood ammonia levels.

When managing other types, do the following.

- *Type II:* Explain test procedures, such as electromyography and EEG, thoroughly.

- *Type III:* Instruct the patient to eat a high-protein diet (eggs, nuts, fish, meat, poultry, and cheese).
- *Type IV:* Watch for signs of hepatic failure (nausea, vomiting, irregular bowel function, clay-colored stools, right upper quadrant pain, jaundice, dehydration, electrolyte imbalance, edema, and changes in mental status, progressing to coma).

When caring for patients with Types II, III, and IV glycogen storage disease, offer the patient and his parents reassurance and emotional support. Recommend and arrange for genetic counseling, if appropriate.

- *Types V through VIII:* Care for these patients is minimal. Explain the disorder to the patient and his family, and help them accept the limitations imposed by his particular type of glycogen storage disease.

Hypoglycemia

Hypoglycemia is an abnormally low glucose level in the bloodstream. It occurs when glucose burns up too rapidly, when the glucose release rate falls behind tissue demands, or when excessive insulin enters the bloodstream. Hypoglycemia is classified as reactive or fasting. *Reactive hypoglycemia* results from the reaction to the disposition of meals or the administration of excessive insulin. *Fasting hypoglycemia* causes discomfort during long periods of abstinence from food, for example, in the early morning before breakfast. Although hypoglycemia is a specific endocrine imbalance, its symptoms are often vague and depend on how quickly the patient's glucose levels drop. If not corrected, severe hypoglycemia may result in coma and irreversible brain damage.

Causes and incidence

Reactive hypoglycemia may take several forms. In a diabetic patient, it may result from administration of too much insulin or, less commonly, too much oral antidiabetic medication. In a mildly diabetic patient (or one in the early stages of diabetes mellitus), reactive hypoglycemia may result from delayed and excessive insulin production

after carbohydrate ingestion. Similarly, a nondiabetic patient may develop reactive hypoglycemia from a sharp increase in insulin output

after a meal. Sometimes called *postprandial hypoglycemia,* this type of reactive hypoglycemia usually disappears when the patient eats something sweet. In some patients, reactive hypoglycemia has no known cause (idiopathic reactive) or may result from gastric dumping syndrome and from impaired glucose tolerance.

Fasting hypoglycemia usually results from an excess of insulin or insulin-like substance or from a decrease in counterregulatory hormones. It can be *exogenous,* resulting from such external factors as alcohol or drug ingestion, or *endogenous,* resulting from organic problems.

Endogenous hypoglycemia may result from tumors or liver disease. Insulinomas, small islet cell tumors in the pancreas, secrete excessive amounts of insulin, which inhibit hepatic glucose production. They're generally benign (in 90% of patients). Extrapancreatic tumors, though uncommon, can also cause hypoglycemia by increasing glucose utilization and inhibiting glucose output. Such tumors occur primarily in the mesenchyma, liver, adrenal cortex, GI system, and lymphatic system. They may be benign or malignant. Among nonendo-crine causes of fasting hypoglycemia are severe liver diseases, including hepatitis, cancer, cirrhosis, and liver congestion associated with heart failure. All of these conditions reduce the uptake and release of glycogen from the liver. Some endocrine causes include adrenocortical insufficiency, which contributes to hypoglycemia by reducing the production of cortisol and cortisone needed for gluconeogenesis; and pituitary insufficiency, which reduces corticotropin and growth hormone levels.

Hypoglycemia is at least as common in neonates and children as it is in adults and affects 1 out of 1,000 people. Usually, infants develop hypoglycemia because of an increased number of cells per unit of body weight and because of increased demands on stored liver glycogen to support respirations, thermoregulation, and muscular activity. In full-term neonates, hypoglycemia may occur 24 to 72 hours after birth and is usually transient. In neonates who are premature or small for gestational age, onset of hypoglycemia is much more rapid (it can occur as soon as 6 hours after birth) because of their small, immature livers, which produce much less glycogen. Maternal disorders that can produce hypoglycemia in neonates within 24 hours after birth include diabetes mellitus, toxemia, erythroblastosis, and glycogen storage disease.

Complication

- Permanent brain damage

Signs and symptoms

Signs and symptoms of reactive hypoglycemia include fatigue, malaise, nervousness, irritability, trembling, tension, headache, hunger, cold sweats, and rapid heart rate. These same clinical effects usually characterize fasting hypoglycemia. In addition, fasting hypoglycemia may also cause central nervous system (CNS) disturbances; for example, blurry or double vision, confusion, motor weakness, hemiplegia, seizures, or coma.

In infants and children, signs and symptoms of hypoglycemia are vague. A neonate's refusal to feed may be the primary clue to underlying hypoglycemia. Associated CNS effects include tremors, twitching, weak or high-pitched cry, sweating, limpness, seizures, and coma.

Diagnosis

A blood glucose monitor or glucose reagent strips provide quick screening methods for determining the blood glucose level. A reading less than 50 mg/dl indicates the need for a venous blood sample. (See *Diagnosing hypoglycemia*.)

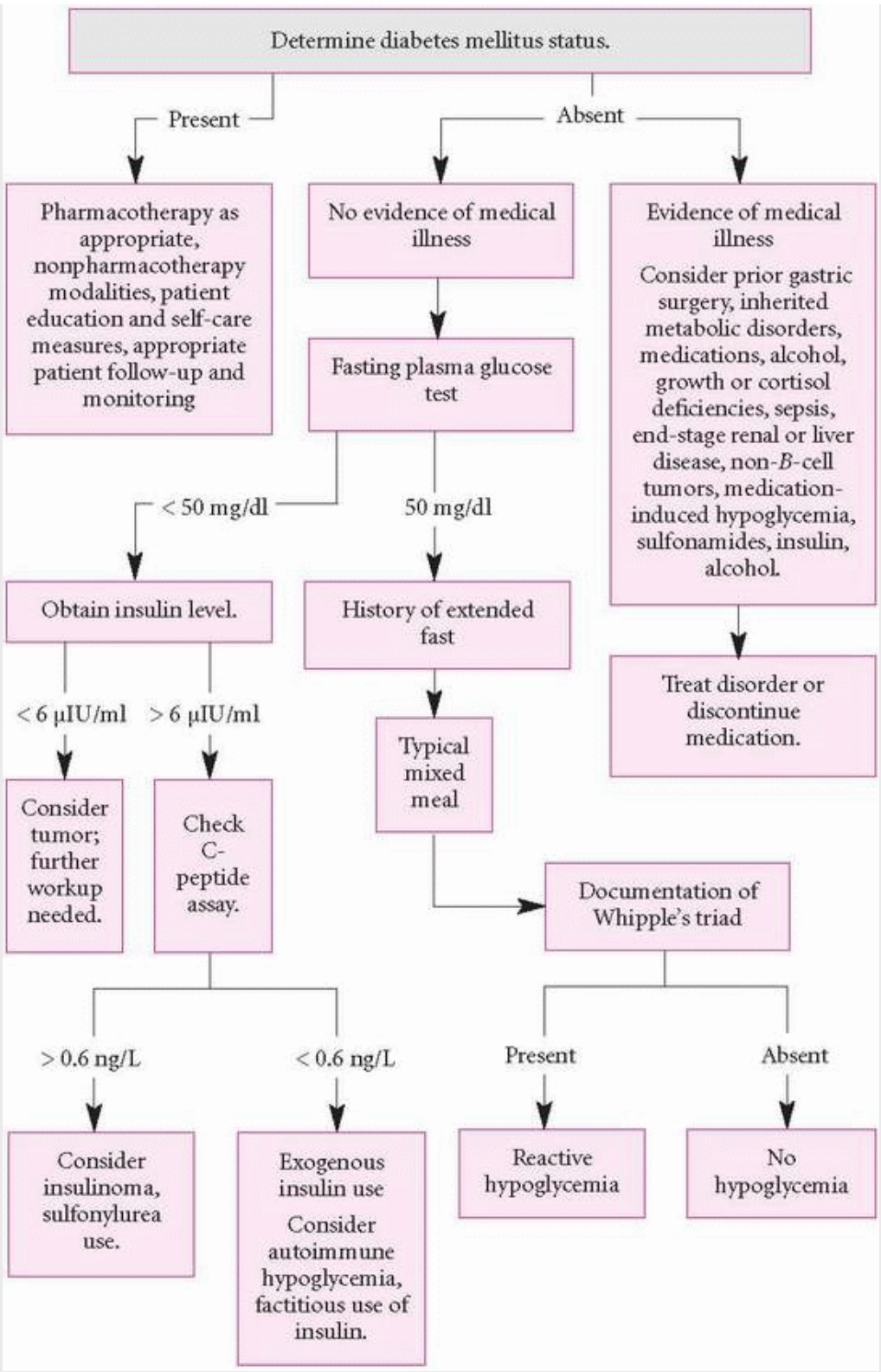
CONFIRMING DIAGNOSIS

Laboratory testing confirms the diagnosis by showing decreased blood glucose levels. The following values indicate hypoglycemia:

- *Full-term infants*
  - less than 30 mg/dl before feeding
  - less than 40 mg/dl after feeding
- *Preterm infants*
  - less than 20 mg/dl before feeding
  - less than 30 mg/dl after feeding

DIFFERENTIAL DIAGNOSIS DIAGNOSING HYPOGLYCEMIA

This flowchart lists possible diagnostic findings and interpretations to assist with treatment of the patient with hypoglycemia.


Determine diabetes mellitus status.
Present
Absent
Pharmacotherapy as appropriate, nonpharmacotherapy modalities, patient education and self-care measures, appropriate patient follow-up and monitoring
No evidence of medical illness
Evidence of medical illness
Consider prior gastric surgery, inherited metabolic disorders, medications, alcohol, growth or cortisol deficiencies, sepsis, end-stage renal or liver disease, non-B-cell tumors, medication-induced hypoglycemia, sulfonamides, insulin, alcohol.
Fasting plasma glucose test
< 50 mg/dl
50 mg/dl
Obtain insulin level.
History of extended fast
Treat disorder or discontinue medication.
< 6 µIU/ml
> 6 µIU/ml
Typical mixed meal
Consider tumor; further workup needed.
Check C-peptide assay.
Documentation of Whipple's triad
> 0.6 ng/L
< 0.6 ng/L
Present
Absent
Consider insulinoma, sulfonylurea use.
Exogenous insulin use
Consider autoimmune hypoglycemia, factitious use of insulin.
Reactive hypoglycemia
No hypoglycemia

- *Children and adults*
    - less than 40 mg/dl before meal
    - less than 50 mg/dl after meal.

In addition, a 5-hour glucose tolerance test may be administered to provoke reactive hypoglycemia. Following a 12-hour fast, laboratory testing to detect plasma insulin and plasma glucose levels may identify fasting hypoglycemia.

Treatment

Effective treatment of reactive hypoglycemia requires dietary modification to help delay glucose absorption and gastric emptying. Usually this includes small, frequent meals; ingestion of complex carbohydrates, fiber, and fat; and avoidance of simple sugars, alcohol, and fruit drinks. The patient may also receive anticholinergic drugs to slow gastric emptying and intestinal motility and to inhibit vagal stimulation of insulin release.

For fasting hypoglycemia, surgery and drug therapy are usually required. In patients with insulinoma, tumor removal is the treatment of choice. Drug therapy may include nondiuretic thiazides such as diazoxide to inhibit insulin secretion; streptozocin; and hormones, such as glucocorticoids and long-acting glycogen.

Therapy for neonates who have hypoglycemia or who are at risk of developing it includes preventive measures. A hypertonic solution of 10% dextrose, calculated at 5 to 10 ml/kg of body weight administered I.V. over 10 minutes and followed by 4 to 8 mg/ kg/minute for maintenance, should correct a severe hypoglycemic state in neonates. To reduce the chance of hypoglycemia in high-risk neonates, they should receive feedings (either breast milk or a solution of 5% to 10% glucose and water) as soon after birth as possible.

Special considerations

- Watch for and report signs of hypoglycemia, such as poor feeding, in high-risk neonates.

- Monitor infusion of hypertonic glucose in the neonate to avoid hyperglycemia, circulatory overload, and cellular dehydration. Terminate glucose solutions gradually to prevent hypoglycemia caused by hyperinsulinemia.
- Explain the purpose and procedure for any diagnostic tests. Collect blood samples at the appropriate times, as ordered.
- Monitor the effects of drug therapy and watch for the development of any adverse effects.
- Teach the patient or his family which foods to include in his diet (complex carbohydrates, fiber, fat) and which foods to avoid (simple sugars, alcohol). Refer the patient and his family for dietary counseling as appropriate.

Hereditary fructose intolerance

Hereditary fructose intolerance is an inability to metabolize fructose. After fructose is eliminated from the diet, symptoms subside within weeks. Older children and adults with hereditary fructose intolerance have normal intelligence and apparently normal liver and kidney function.

Causes and incidence

Transmitted as an autosomal recessive trait, hereditary fructose intolerance results from a deficiency in the enzyme fructose-1-phosphate aldolase. The enzyme operates at only 1% to 10% of its normal biological activity, thus preventing rapid uptake of fructose by the liver after ingestion of fruit or foods containing cane sugar.

In some European countries, hereditary fructose intolerance may have an incidence as high as 1 in 20,000 people.

Signs and symptoms

Typically, clinical features of hereditary fructose intolerance appear shortly after dietary introduction of foods containing fructose or sucrose. Symptoms are more severe in infants than in older people and include hypoglycemia, nausea, vomiting, pallor, excessive sweating,

cyanosis, and tremor. In neonates and young children, continuous ingestion of foods containing fructose may result in failure to thrive, hypoglycemia, jaundice, hyperbilirubinemia, ascites, hepatomegaly, vomiting, dehydration, hypophosphatemia, albuminuria, aminoaciduria, seizures, coma, febrile episodes, substernal pain, and anemia.

Diagnosis

A dietary history often suggests hereditary fructose intolerance.

CONFIRMING DIAGNOSIS

A fructose tolerance test (using glucose oxidase or paper chromatography to measure glucose levels) usually confirms the diagnosis. However, liver biopsy showing a deficiency in fructose-1-phosphate aldolase may be necessary for a definitive diagnosis.

Supportive values may include decreased serum inorganic phosphorus levels. Urine studies may show fructosuria and albuminuria.

Treatment

Treatment of hereditary fructose intolerance consists of exclusion of fructose and sucrose (cane sugar or table sugar) from the diet. Otherwise, treatment is supportive as the patient's progress is monitored.

Special considerations

- Tell the patient to avoid fruits containing fructose and vegetables containing sucrose (sugar beets, sweet potatoes, and peas), because sucrose is digested to glucose and fructose in the intestine. Fruits containing the least amount of fructose include strawberries, blackberries, blueberries, oranges, and grapefruits; others low in fructose are cherries, pears, bananas, grapes, and apples.
- Refer the patient and his family for genetic and dietary counseling as appropriate.

Hyperlipoproteinemia

Hyperlipoproteinemia occurs as five distinct metabolic disorders, all of which may be inherited. Types I and III are transmitted as autosomal recessive traits; Types II, IV, and V are transmitted as autosomal dominant traits. (See *Types of hyperlipoproteinemia, page 572.*) About one in five persons with elevated plasma lipid and lipoprotein levels has hyperlipoproteinemia. It's marked by increased plasma concentrations of one or more lipoproteins. Hyperlipoproteinemia may also occur secondary to other conditions, such as diabetes, pancreatitis, hypothyroidism, or renal disease.

Causes and incidence

This disorder affects lipid transport in serum and produces varied clinical changes, from relatively mild symptoms that can be corrected by dietary management to potentially fatal pancreatitis.

Complications

- Coronary artery disease
- Pancreatitis

Signs and symptoms

- *Type I:* recurrent attacks of severe abdominal pain similar to pancreatitis, usually preceded by fat intake; abdominal spasm, rigidity, or rebound tenderness; hepatosplenomegaly, with liver or spleen tenderness; papular or eruptive xanthomas (pinkish-yellow cutaneous deposits of fat) over pressure points and extensor surfaces; lipemia retinalis (reddish-white retinal vessels); malaise; anorexia; and fever
- *Type II:* tendinous xanthomas (firm masses) on the Achilles tendons and tendons of the hands and feet, tuberous xanthomas, xanthelasma, juvenile corneal arcus (opaque ring surrounding the corneal periphery), accelerated atherosclerosis and premature coronary artery disease, and recurrent polyarthritis and tenosynovitis

- *Type III:* peripheral vascular disease manifested by claudication or tuboeruptive xanthomas (soft, inflamed, pedunculated lesions) over the elbows and knees; palmar xanthomas on the hands, particularly the fingertips; premature atherosclerosis
- *Type IV:* predisposition to atherosclerosis and early coronary artery disease, exacerbated by excessive calorie intake, obesity, diabetes, and hypertension
- *Type V:* abdominal pain (most common), pancreatitis, peripheral neuropathy, eruptive xanthomas on extensor surfaces of the arms and legs, lipemia retinalis, and hepatosplenomegaly.

Treatment

The first goal is to identify and treat any underlying problem such as diabetes. If no underlying problem exists, the primary treatment of Types II, III, and IV is dietary management, especially restriction of cholesterol intake, possibly supplemented by drug therapy (cholestyramine, clofibrate, niacin) to lower plasma triglyceride or cholesterol level when diet alone is ineffective.

TYPES OF HYPERLIPOPROTEINEMIA

Type	Causes and incidence	Diagnostic findings
I (Frederickson's hyperlipoproteinemia, fat-induced hyperlipemia, idiopathic familial)	▪ Deficient or abnormal lipoprotein lipase, resulting in decreased or absent post-heparin lipolytic activity ▪ Relatively rare ▪ Present at birth	▪ Chylomicrons (very-low-density lipoprotein [VLDL], low-density lipoprotein [LDL], high-density lipoprotein), in plasma 14 hours or more after last meal ▪ Highly elevated serum chylomicrons and triglyceride levels; slightly elevated serum cholesterol levels

		▪ Lower serum lipoprotein lipase levels ▪ Leukocytosis
II (familial hyperbetalipoproteinemia, essential familial hypercholesterolemia)	▪ Deficient cell surface receptor that regulates LDL degradation and cholesterol synthesis, resulting in increased levels of plasma LDL over joints and pressure points ▪ Onset between ages 10 and 30	▪ Increased plasma concentrations of LDL ▪ Increased serum LDL and cholesterol levels ▪ Amniocentesis shows increased LDL levels
III (familial broadbeta disease, dysbetalipoproteinemia, remnant removal disease, xanthoma tuberosum)	▪ Unknown underlying defect results in deficient conversion of triglyceriderich VLDL to LDL ▪ Uncommon; usually occurs after age 20 but can occur earlier in men	▪ Abnormal serum beta-lipoprotein ▪ Elevated cholesterol and triglyceride levels ▪ Slightly elevated glucose tolerance ▪ Hyperuricemia
IV (endogenous hypertriglyceridemia, hyperbetalipoproteinemia)	▪ Usually occurs secondary to obesity, alcoholism, diabetes, or emotional disorders ▪ Relatively common, especially in middle-age men	▪ Elevated VLDL levels ▪ Abnormal levels of triglycerides in plasma; variable increase in serum ▪ Normal or slightly elevated serum cholesterol levels ▪ Mildly abnormal glucose tolerance ▪ Family history ▪ Early coronary artery disease
V		

(mixed hypertriglyceridemia, mixed hyperlipidemia)	▪ Defective triglyceride clearance causes pancreatitis; usually secondary to another disorder, such as obesity or nephrosis ▪ Uncommon; onset usually occurs in late adolescence or early adulthood	▪ Chylomicrons in plasma ▪ Elevated plasma VLDL levels ▪ Elevated serum cholesterol and triglyceride levels

Type I hyperlipoproteinemia requires long-term weight reduction, with fat intake restricted to less than 20 g/day. A 20- to 40-g/day medium-chain triglyceride diet may be ordered to supplement calorie intake. The patient should also avoid alcoholic beverages, to decrease plasma triglyceride levels. The prognosis is good with treatment; without treatment, death can result from pancreatitis.

For Type II, dietary management to restore normal lipid levels and decrease the risk of atherosclerosis includes restriction of cholesterol intake to less than 300 mg/ day for adults and less than 150 mg/day for children; triglycerides must be restricted to less than 100 mg/day for children and adults. Diet should also be high in polyunsaturated fats. In familial hypercholesterolemia, nicotinic acid with a bile acid usually normalizes low-density lipoprotein levels. For severely affected children, a portacaval shunt is a last resort to reduce plasma cholesterol levels. The prognosis remains poor regardless of treatment; in homozygotes, myocardial infarction usually causes death before age 30.

For Type III, dietary management includes restriction of cholesterol intake to less than 300 mg/day; carbohydrates must also be restricted, while polyunsaturated fats are increased. Clofibrate and niacin help lower blood lipid levels. Weight reduction is helpful. With strict adherence to prescribed diet, the prognosis is good.

For Type IV, weight reduction may normalize blood lipid levels without additional treatment. Long-term dietary management includes restricted cholesterol intake, increased polyunsaturated fats, and avoidance of alcoholic beverages. Clofibrate and niacin may lower plasma lipid levels. The prognosis remains uncertain, however, because of predisposition to premature coronary artery disease.

The most effective treatment for Type V is weight reduction and long-term maintenance of a low-fat diet. Alcoholic beverages must be avoided. Niacin, clofibrate, gemfibrozil, and a 20- to 40-g/day medium-chain triglyceride diet may prove helpful. The prognosis is uncertain because of the risk of pancreatitis. Increased fat intake may cause recurrent bouts of illness, possibly leading to pseudocyst formation, hemorrhage, and death.

USING BILE ACID SEQUESTRANTS

Before giving the patient a bile acid sequestrant, such as cholestyramine, to lower cholesterol levels, make certain he isn't taking a drug whose absorption is affected by bile acid sequestrants. For example, bile acid sequestrants decrease the absorption of diuretics such as chlorothiazide. Other drugs affected besides diuretics include:

- beta-adrenergic blockers
- digitoxin
- fat-soluble vitamins
- folic acid
- thiazides
- thyroxine
- warfarin.

Special considerations

Nursing care for hyperlipoproteinemia emphasizes careful monitoring for adverse drug effects and teaching the importance of long-term dietary management.

- Administer cholestyramine before meals or before bedtime. This drug must not be given with other medications. (See *Using bile acid sequestrants*.) Watch for adverse effects, such as nausea, vomiting, constipation, steatorrhea, rashes, and hyperchloremic acidosis. Also watch for malabsorption of other medications and fat-soluble vitamins.

- Give clofibrate as ordered. Watch for adverse effects, such as cholelithiasis, cardiac arrhythmias, intermittent claudication, thromboembolism, nausea, weight gain (from fluid retention), and myositis.

ALERT

Don't administer niacin to patients with active peptic ulcers or hepatic disease. Use with caution in patients with diabetes. In other patients, watch for adverse effects, such as flushing,

pruritus, hyperpigmentation, and exacerbation of inactive peptic ulcers.

- Urge the patient to adhere to the ordered diet (usually 1,000 to 1,500 calories/day) and to avoid excess sugar and alcoholic beverages, to minimize his intake of saturated fats (higher in meats, coconut oil), and to increase his intake of polyunsaturated fats (vegetable oils).
- Instruct the patient, for the 2 weeks preceding serum cholesterol and serum triglyceride tests, to maintain a steady weight and to adhere strictly to the prescribed diet. He should also fast for 12 hours preceding the test.
- Instruct women with elevated serum lipid levels to avoid hormonal contraceptives or drugs that contain estrogen.

Gaucher's disease

Gaucher's disease, the most common lysosomal storage disease, causes an abnormal accumulation of glucocerebrosides in reticuloendothelial cells. It occurs in three forms: Type I (adult); Type II (infantile); and Type III (juvenile). Type II can prove fatal within 9 months of onset, usually from pulmonary involvement.

Causes and incidence

Gaucher's disease results from an autosomal recessive inheritance, which causes decreased activity of the enzyme glucocerebrosidase. Glucocerebrosidase deficiency leads to an accumulation of glucosylceramide in the storage compartments (lysosomes) of certain body cells. Glucosylceramide buildup occurs in the liver, spleen, bones, and bone marrow, eventually leading to decreased production of red blood cells (anemia) and thinning of the bones (osteopenia).

There are three forms of Gaucher's disease, classified by age of onset and the presence or absence of neurologic involvement. Type I, characterized by lack of neurologic involvement, is the most common form affecting both children and adults and is most prevalent in the Ashkenazi Jewish population, affecting anywhere from 1 of 500 to 1,000 births. Type II usually presents in infancy with severe neurologic involvement, resulting in seizures and central nervous system damage. Type II also presents with spleen and bone marrow damage. Type III typically has mild neurologic involvement and runs a slower, more favorable course. The incidence of Types II and III is 1 of 50,000 to 100,000 births. The juvenile form can begin in childhood, typically in the teenage years, and cause spleen, bone marrow, and neurologic damage.

Complications

- Neurologic impairment
- Portal hypertension
- Pathological fractures
- Anemia
- Respiratory failure (Type II)

Signs and symptoms

The key signs of all types of Gaucher's disease are hepatosplenomegaly and bone lesions. In Type I, bone lesions lead to thinning of cortices, pathologic fractures, collapsed hip joints and, eventually, vertebral compression. Severe episodic pain may develop in the legs, arms, and back but usually not until adolescence. (The adult form of Gaucher's disease is generally diagnosed while the patient is in his teens; the word “adult” is used loosely here.) Other clinical effects of Type I are fever,

abdominal distention (from hypotonicity of the large bowel), respiratory problems (pneumonia or, rarely, cor pulmonale), easy bruising and bleeding, anemia and, rarely, pancytopenia. Older patients may develop a yellow pallor and brown-yellow pigmentation on the face and legs.

In Type II, motor dysfunction and spasticity occur at age 6 to 7 months. Other signs of the infantile form of Gaucher's disease include abdominal distention, strabismus, muscle hypertonicity, retroflexion of the head, neck rigidity, dysphagia, laryngeal stridor, hyperreflexia, seizures, respiratory distress, and easy bruising and bleeding.

Clinical effects of Type III after infancy include seizures, hypertonicity, strabismus, poor coordination and mental ability and, possibly, easy bruising and bleeding.

Diagnosis

CONFIRMING DIAGNOSIS

Bone marrow aspiration showing Gaucher's cells and direct assay of glucocerebrosidase activity, which can be performed on venous blood, confirms this diagnosis.

Supportive laboratory results include increased serum acid phosphatase level, decreased platelets and serum iron level and, in Type III, abnormal EEG after infancy.

Treatment

Treatment is mainly supportive and consists of vitamins, supplemental iron or liver extract to prevent anemia caused by iron deficiency and to alleviate other hematologic problems, blood transfusions for anemia, splenectomy for thrombocytopenia, and strong analgesics for bone pain. Injections of a replacement synthetic enzyme have proven helpful. Gene therapy is an experimental approach. An oral treatment with N-butyl deoxynojirimycin (OGT 918), which inhibits glucocerebrosidase formation, is being evaluated. Clinical trials have shown improvement in the key clinical features of Gaucher's disease, including liver and spleen size and, to a lesser degree, blood counts.

Special considerations

- In the patient confined to bed, prevent pathologic fractures by turning him carefully. If he is ambulatory, make sure that he's assisted when getting out of bed or walking.
- Observe closely for changes in pulmonary status.
- Explain all diagnostic tests and procedures to the patient or his parents. Help the patient accept the limitations imposed by this disorder.
- Recommend genetic counseling for patients with a family history of Gaucher's disease. Prenatal testing can determine if a fetus has the syndrome.

Porphyrias

Porphyrias are metabolic disorders that affect the biosynthesis of heme (a component of hemoglobin) and cause excessive production and excretion of porphyrins or their precursors. Porphyrins, which are present in all protoplasm, figure prominently in energy storage and utilization. Classification of porphyrias depends on the site of excessive porphyrin production; they may be erythropoietic (erythroid cells in bone marrow), hepatic (in the liver), or erythrohepatic (in bone marrow and liver). (See *Types of porphyria,* pages 576 and 577.) An acute episode of intermittent hepatic porphyria may cause fatal respiratory paralysis. In the other forms of porphyrias, the prognosis is good with proper treatment.

PREVENTION

PREVENTING PORPHYRIA

Precipitating factors may lead to signs and symptoms of porphyria. Encourage the patient to avoid:

- crash dieting
- fasting
- specific drugs such as alcohol, barbiturates, and estrogens

- stress
- infection.

Helpful hints

- Stress management techniques may help because emotional stress may also precipitate an attack.
- Reduce infection risk with proper hand washing and avoiding people with known infection.
- Genetic counseling may also be of benefit to prospective parents with a family history of porphyria.

Causes and incidence

Porphyrias are inherited as autosomal dominant traits, except for Günther's disease (autosomal recessive trait) and toxic-acquired porphyria (usually from ingestion of or exposure to lead). Menstruation often precipitates acute porphyria in premenopausal women. (See *Preventing porphyria*.)

TYPES OF PORPHYRIA

Porphyria	Signs and symptoms	Treatment
Erythropoietic porphyria		
Günther's disease		
▪ Usual onset before age 5	▪ Red urine (earliest, most characteristic sign); severe cutaneous photosensitivity, leading to vesicular or bullous eruptions on exposed areas and, eventually, scarring and ulceration ▪ Hypertrichosis ▪ Brown-stained or redstained teeth ▪ Splenomegaly, hemolytic anemia	▪ Oral beta-carotene to prevent photosensitivity reactions ▪ Anti-inflammatory ointments ▪ Prednisone to reverse anemia ▪ Packed red cells to inhibit erythropoiesis

		and excreted porphyrins ▪ Hemin for recurrent attacks ▪ Splenectomy for hemolytic anemia ▪ Topical dihydroxyacetone and lawsone sunscreen filter
Erythrohepatic porphyria		
Protoporphyria		
▪ Usually affects children ▪ Occurs most often in males	▪ Photosensitive dermatitis ▪ Hemolytic anemia ▪ Chronic hepatic disease	▪ Avoidance of causative factors ▪ Beta-carotene to reduce photosensitivity
Toxic-acquired porphyria		
▪ Usually affects children ▪ Significant mortality	▪ Acute colicky pain ▪ Anorexia, nausea, vomiting ▪ Neuromuscular weakness ▪ Behavioral changes ▪ Seizures, coma	▪ Chlorpromazine I.V. to relieve pain and GI symptoms ▪ Avoidance of lead exposure
Hepatic porphyria		
Acute intermittent porphyria		
▪ Most common form ▪ Affects females most often, usually	▪ Colicky abdominal pain with fever, general malaise, and hypertension ▪ Peripheral neuritis, behavioral changes, possibly leading to frank psychosis ▪ Possible respiratory paralysis	▪ Chlorpromazine I.V. to relieve abdominal pain and control psychic abnormalities

between ages 15 and 40		▪ Avoidance of barbiturates, infections, alcohol, and fasting ▪ Hemin for recurrent attacks ▪ High-carbohydrate diet
Variegate porphyria		
▪ Usual onset between ages 30 and 50 ▪ Occurs almost exclusively among South African whites ▪ Affects males and females equally	▪ Skin lesions, extremely fragile skin in exposed areas ▪ Hypertrichosis ▪ Hyperpigmentation ▪ Abdominal pain during acute attack ▪ Neuropsychiatric manifestations	▪ High-carbohydrate diet ▪ Avoidance of sunlight, or wearing protective clothing when avoidance isn't possible ▪ Hemin for recurrent attacks
Porphyria cutanea tarda		
▪ Most frequent in men ages 40 to 60 ▪ Highest incidence in South Africans	▪ Facial pigmentation ▪ Red-brown urine ▪ Photosensitive dermatitis ▪ Hypertrichosis	▪ Avoidance of precipitating factors, such as alcohol and estrogens ▪ Phlebotomy at 2-week intervals to lower serum iron level
Hereditary coproporphyria		
▪ Rare ▪ Affects males and females	▪ Asymptomatic or mild neurologic, abdominal, or psychiatric symptoms	▪ High-carbohydrate diet

equally	▪ Avoidance of barbiturates ▪ Hemin for recurrent attacks

Complications

- Neurologic and hepatic dysfunction (hepatic)
- Cholelithiasis
- Coma
- Flaccid paralysis, respiratory paralysis, and death (acute intermittent)
- Hemolytic anemia (erythropoietic)

Signs and symptoms

Porphyrias are generally marked by photosensitivity, acute abdominal pain, and neuropathy. Hepatic porphyrias may produce a complex syndrome marked by distinct neurologic and hepatic dysfunction:

- Neurologic symptoms include chronic brain syndrome, peripheral neuropathy and autonomic effects, tachycardia, labile hypertension, severe colicky lower abdominal pain, and constipation.
- During an acute attack, fever, leukocytosis, and fluid and electrolyte imbalance may occur.
- Structural hepatic effects include fatty infiltration of the liver, hepatic siderosis, and focal hepatocellular necrosis.
- Skin lesions may cause itching and burning, erythema, and altered pigmentation and edema in areas exposed to light. Some chronic skin changes include milia (white papules on the hands' dorsal aspects) and hirsutism on the upper cheeks and periorbital areas.

Diagnosis

CONFIRMING DIAGNOSIS

Generally, diagnosis requires screening tests for porphyrins or their precursors (such as aminolevulinic acid [ALA] and porphobilinogen [PBG]) in urine, stool, blood or, occasionally, skin biopsy. A urinary lead level of 0.2 mg/L confirms toxic-acquired porphyria.

Other laboratory values may include increased serum iron levels in porphyria cutanea tarda; leukocytosis, syndrome of inappropriate antidiuretic hormone, and

elevated bilirubin and alkaline phosphatase levels in acute intermittent porphyria.

DRUGS THAT AGGRAVATE PORPHYRIA

Make sure the patient with porphyria doesn't receive any of the following drugs, which are known to precipitate signs and symptoms of porphyria:

- Alcohol
- Barbiturates
- Carbamazepine
- Carisoprodol
- Chloramphenicol
- Chlordiazepoxide
- Danazol
- Diazepam
- Ergot alkaloids
- Estrogens
- Griseofulvin
- Imipramine
- Meprobamate
- Methsuximide
- Methyldopa

- Pentazocine
- Phenytoin
- Progesterones
- Sulfonamides
- Tolbutamide

Treatment

Treatment for porphyrias includes avoiding overexposure to the sun and using beta-carotene to reduce photosensitivity, as well as support for acute and long-term management. Hemin (an enzyme-inhibitor derived from processed red blood cells) is given to control recurrent attacks of acute intermittent porphyria, Günther's disease, variegate porphyria, and hereditary coproporphyria. A high-carbohydrate diet decreases urinary excretion of ALA and PBG, with restricted fluid intake to inhibit release of antidiuretic hormone.

Special considerations

- Warn the patient to avoid excessive sun exposure, use a sunscreen when outdoors, and take a beta-carotene supplement to reduce photosensitivity.
- Encourage a high-carbohydrate diet.
- Administer beta-carotene and hemin, as ordered.
- Advise the patient to avoid drugs that may precipitate signs and symptoms of porphyrias. (See *Drugs that aggravate porphyria*.)

Metabolic syndrome

Metabolic syndrome—also called *syndrome X, insulin resistance syndrome, dysmetabolic syndrome,* and *multiple metabolic syndrome* — is a cluster of conditions characterized by abdominal obesity, high blood glucose (type 2 diabetes mellitus), insulin resistance, high blood cholesterol and triglycerides, and high blood pressure. More than 22% of people in the United States meet three or more of these criteria, raising

their risk of heart disease and stroke and placing them at high risk for dying of myocardial infarction.

In the normal digestion process, the intestines break down food into its basic components, one of which is glucose. Glucose provides energy for cellular activity, while excess glucose is stored in cells for future use. Insulin, a hormone secreted in the pancreas, guides glucose into storage cells. However, in people with metabolic syndrome, glucose is insulin-resistant and doesn't respond to insulin's attempt to guide it into storage cells. Excess insulin is then required to overcome this resistance. This excess in quantity and force of insulin causes damage to the lining of the arteries, promotes fat storage deposits, and prevents fat breakdown. This series of events can lead to diabetes, blood clots, and coronary events.

Causes and incidence

Abdominal obesity is a strong predictor of metabolic syndrome because abdominal fat tends to be more resistant to insulin than fat in other areas. This increases the release of free fatty acid into the portal system, leading to increased apolipoprotein B, increased low-density lipoprotein (LDL), decreased high-density lipoprotein (HDL), and increased triglyceride levels. As a result, the risk of cardiovascular disease is increased.

Type 2 diabetes mellitus is a risk factor because a hallmark for metabolic syndrome is a fasting glucose level greater than 110 mg/dl. People with diabetes develop atherosclerotic heart disease at a younger age than other people. They're also at increased risk of macrovascular disease (ischemic heart disease, stroke, and peripheral vascular disease). Diabetes is a coronary heart disease risk equivalent.

Insulin resistance and dyslipidemia are also risk factors because insulin resistance leads to hyperinsulinemia, hyperglycemia, abnormal glucose and lipid metabolism, damaged endothelium, and cardiovascular disease. Insulin is also responsible for reducing the amount of free fatty acids in the liver. However, people with insulin resistance have an increased amount of free fatty acids reaching the liver, resulting in high

triglycerides and LDLs and producing an abnormal endothelium and atherosclerosis.

High blood pressure is a risk factor because the combination of insulin resistance, hyperinsulinemia, and abdominal obesity leads to hypertension and its harmful cardiovascular effects. Moreover, insulin resistance promotes salt sensitivity in people with high blood pressure.

Research also indicates that there may be a genetic predisposition to metabolic syndrome.

Complications

- Coronary artery disease
- Diabetes mellitus
- Hyperlipidemia

Signs and symptoms

Assessment commonly reveals a history of hypertension, abdominal obesity, sedentary lifestyle, poor diet, and a family history of metabolic syndrome. Physical findings include abdominal obesity (evidenced by a waist of more than 40″ [101.6 cm] in men and 35″ [88.9 cm] in women), blood pressure 130/85 mm Hg or higher, and a fasting blood glucose level that's 100 mg/dl or higher. The patient may feel tired, especially after eating, and may have difficulty losing weight. If left untreated, such complications as coronary artery disease, diabetes, hyperlipidemia, and premature death may develop.

Diagnosis

Blood studies commonly indicate elevated blood glucose levels, hyperinsulinemia, and elevated serum uric acid. Use of lipid profile studies reveal elevated LDL levels, low HDL levels, and elevated triglycerides. Further diagnostic procedures are nonspecific, but may be performed to detect hypertension, diabetes, hyperlipidemia, and hyperinsulinemia.

Treatment

Lifestyle modification, focusing on weight reduction and exercise, is an important part of the treatment regimen. Modest weight reduction through diet and exercise considerably improves hemoglobin A_{1c} levels, reduces insulin resistance, improves blood lipid levels, and decreases blood pressure—all elements of metabolic syndrome. Recent studies have shown that in patients with impaired glucose tolerance, losing an average of 7% of body weight reduced the risk of developing type 2 diabetes by 58%.

To improve cardiovascular health, a diet rich in vegetables, fruits, whole grains, fish, and low-fat dairy products combined with regular exercise is recommended. Moreover, nutrient-dense, low-energy foods should replace low-nutrient, high-calorie foods. Meal replacements and shakes may also reduce risk factors for metabolic syndrome and improve weight loss. (See *Therapeutic lifestyle-change diet*, page 580.)

A regular exercise program of moderate physical activity, in addition to dietary modifications, promotes weight loss, improves insulin sensitivity, and reduces blood glucose levels. According to the Surgeon General's Report on Physical Activity and Health, a person should exercise moderately for a minimum of 30 minutes on most (if not all) days of the week. The selected exercise program should improve cardiovascular conditioning, increase strength through resistance training, and improve flexibility.

Medications may be used in the treatment of metabolic syndrome for patients who have a body mass index (BMI) of 27 kg/m2 or greater in the presence of other risk factors (such as diabetes, hypertension, and hyperlipidemia) or for patients

with a BMI of 30 kg/m^2 or greater without other risk factors. Weight loss drugs may also be added to lifestyle changes if the patient hasn't achieved significant weight loss after 12 weeks.

THERAPEUTIC LIFESTYLE-CHANGE DIET

The therapeutic lifestyle-change diet is low in saturated fats and cholesterol to reduce blood cholesterol levels and prevent development of heart disease and its complications.

Nutrient	Recommended intake
Saturated fat*	< 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25% to 35% of total calories
Carbohydrate**	50% to 60% of total calories
Fiber	20 to 30 gm/day
Protein	Approximately 15% of total calories
Cholesterol	< 200 mg/day
Total calories***	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain

* Trans fatty acids are another low-density lipoprotein-raising fat that should be minimized or avoided.

** Carbohydrates should be derived predominantly from foods rich in complex carbohydrates, including grains—especially whole grains, fruits, and vegetables.

*** Daily expenditure should include at least moderate physical activity (contributing about 200 kcal/day).

Source: The National Heart, Blood, and Lung Institute. Available at: *www.nhlbi.nih.gov/chd/lifestyles.htm.*

Pharmacologic treatment may also be indicated. Phentermine is used for short-term treatment of obesity in conjunction with diet and exercise. The only two drugs that have been approved for long-term weight loss are orlistat (Xenical) and sibutramine (Meridia). Orlistat works by decreasing the absorption of dietary fat by inhibiting pancreatic lipase,

which is needed for fat breakdown and absorption. However, because absorption of fat-soluble vitamins is reduced, the patient may require vitamin supplementation. Studies show that when obese patients take orlistat in conjunction with dieting, they achieve greater weight loss and serum glucose control than by dieting alone. Sibutramine promotes weight loss by inhibiting the reuptake of serotonin, norepinephrine, and dopamine and increases the satietyproducing effects of serotonin. Further, it reduces the drop in metabolic rate that commonly occurs with weight loss.

Surgical treatment of obesity, such as through gastric bypass procedures, produces a greater degree and duration of weight loss than other therapies and improves or resolves most of the factors of metabolic syndrome. Candidates for surgical intervention include patients with a BMI greater than 40 kg/m2 or those with a BMI greater than 35 kg/m2 with obesity-related medical conditions. Gastric bypass procedures produce permanent weight loss in the majority of patients.

Special considerations

- Monitor the patient's blood pressure, blood glucose, blood cholesterol, and insulin levels.
- Because research indicates that longer lifestyle modification programs are associated with improved weight loss maintenance, encourage patients with metabolic syndrome to begin an exercise and weight loss program with a friend or family member. Assist him in exploring options and support his efforts.

- To improve compliance, schedule frequent follow-up appointments with the patient. At that time, review his food diaries and exercise logs. Be positive and promote his active participation and partnership in his treatment plan.
- A patient planning gastric bypass surgery should receive psychological and nutritional counseling before and after the surgery to assit with diet and lifestyle changes.

HOMEOSTATIC IMBALANCE

Potassium imbalance

Potassium, a cation that's the dominant cellular electrolyte, facilitates contraction of both skeletal and smooth muscles—including myocardial contraction—and figures prominently in nerve impulse conduction, acid-base balance, enzyme action, and cell membrane function. Because serum potassium level has such a narrow range (3.5 to 5 mEq/L), a slight deviation in either direction can produce profound clinical consequences. Paradoxically, both hypokalemia (potassium deficiency) and hyperkalemia (potassium excess) can lead to muscle weakness and flaccid paralysis, because both create an ionic imbalance in neuromuscular tissue excitability. Both conditions also diminish excitability and conduction rate of the heart muscle, which may lead to cardiac arrest. (See *Clinical effects of potassium imbalance,* page 582.)

Causes and incidence

Because many foods contain potassium, hypokalemia seldom results from a dietary deficiency. Instead, potassium loss may result from:

- excessive GI losses, such as diarrhea, dehydration, anorexia, or chronic laxative abuse (Vomiting and gastric suction cause dehydration, resulting in hyperaldosteronism [sodium retention and potassium excretion occur].)
- trauma (injury, burns, or surgery), in which damaged cells release potassium, which enters serum or extracellular fluid, to be excreted in the urine
- chronic renal disease, with tubular potassium wasting
- certain drugs, especially potassium-wasting diuretics, steroids, and certain sodium-containing antibiotics (carbenicillin)
- acid-base imbalances, which cause potassium shifting into cells without true depletion in alkalosis
- prolonged potassium-free I.V. therapy
- hyperglycemia, causing osmotic diuresis and glycosuria
- Cushing's syndrome, primary hyperaldosteronism, excessive licorice ingestion, and severe serum magnesium deficiency.

Hyperkalemia results from the kidneys' inability to excrete excessive amounts of potassium infused I.V. or administered orally; from decreased urine output, renal dysfunction or failure; or the use of potassium-sparing diuretics, such as triamterene, by patients with renal disease. It may also result from any injuries or conditions that release cellular potassium or favor its retention, such as burns, crushing injuries, failing renal function, adrenal gland insufficiency, dehydration, or diabetic acidosis.

Complications

- Muscle weakness
- Flaccid paralysis
- Cardiac arrest

Diagnosis

CONFIRMING DIAGNOSIS

Serum potassium levels less than 3.5 mEq/L confirm hypokalemia; serum levels greater than 5 mEq/L confirm hyperkalemia.

Additional tests may be necessary to determine the imbalance's underlying cause. Hypokalemia is also associated with hypomagnesemia, so further study of other electrolytes is warranted.

Treatment

For hypokalemia, replacement therapy with potassium chloride (I.V. or orally) is the primary treatment. When diuresis is necessary, spironolactone, a potassium-sparing diuretic, may be administered concurrently with a potassium-wasting diuretic to minimize potassium loss. Hypokalemia can be prevented by giving a maintenance dose of potassium I.V. to patients who may not take anything by mouth and to others predisposed to potassium loss.

CLINICAL EFFECTS OF POTASSIUM IMBALANCE

Dysfunction	Hypokalemia	Hyperkalemia
Acid-base balance	▪ Metabolic alkalosis	▪ Metabolic acidosis
Cardiovascular	▪ Dizziness, hypotension, arrhythmias, electrocardiogram (ECG) changes (flattened T waves, elevated U waves, depressed ST segment), cardiac arrest (with serum potassium levels < 2.5 mEq/L)	▪ Tachycardia and later bradycardia, ECG changes (tented and elevated T waves, widened QRS complex, prolonged PR interval, flattened or absent P waves, depressed ST segment), cardiac arrest (with levels > 7 mEq/L)
Gastrointestinal	▪ Nausea, vomiting, anorexia, diarrhea, abdominal distention, paralytic ileus or decreased peristalsis	▪ Nausea, diarrhea, abdominal cramps
Genitourinary	▪ Polyuria	▪ Oliguria, anuria
Musculoskeletal	▪ Muscle weakness and fatigue, leg cramps	▪ Muscle weakness, flaccid paralysis
Neurologic	▪ Malaise, irritability, confusion, mental depression, speech changes, decreased reflexes, respiratory paralysis	▪ Hyperreflexia progressing to weakness, numbness, tingling, flaccid paralysis

For hyperkalemia, rapid infusion of 10% calcium gluconate decreases myocardial irritability and temporarily prevents cardiac arrest but doesn't correct serum potassium excess; it's also contraindicated in patients receiving cardiac glycosides. As an emergency measure, sodium bicarbonate I.V. increases pH and causes potassium to shift back into the cells. Insulin and 10% to 50% glucose I.V. also move potassium back into cells. Infusions should be followed by dextrose 5% in water because infusion of 10% to 15% glucose will stimulate endogenous insulin secretion. Sodium polystyrene sulfonate with 70% sorbitol produces exchange of sodium ions for potassium ions in the intestine. Hemodialysis or peritoneal dialysis also aids in removal of excess potassium.

Special considerations

For hypokalemia:

- Check serum potassium and other electrolyte levels in patients apt to develop potassium imbalance and in those requiring potassium replacement; they risk overcorrection to hyperkalemia.
- Assess intake and output carefully. Remember, the kidneys excrete 80% to 90% of ingested potassium. Never give supplementary potassium to a patient whose urine output is below 600 ml/day. Also, measure GI loss from suctioning or vomiting.
- Administer slow-release potassium or dilute oral potassium supplements in 4 oz (118 ml) or more of water or other fluid to reduce gastric and small-bowel irritation. Determine the patient's chloride level. As ordered, give a potassium chloride supplement

  if the level is low; potassium gluconate if it's normal.
- Give potassium I.V. only after it's diluted in solution (usually, 10 mEq/100 ml of fluid); potassium is very irritating to vascular, subcutaneous, and fatty tissues and may cause phlebitis or tissue necrosis if it infiltrates. Infuse slowly (no more than 20 mEq/ L/hour through central administration or 10 mEq/hour through peripheral administration) to prevent hyperkalemia.

ALERT

Never administer by I.V. push or bolus; it may cause cardiac arrest.

- Carefully monitor patients receiving cardiac glycosides because hypokalemia enhances the action of these drugs and may produce signs of digoxin toxicity (anorexia, nausea, vomiting, blurred vision, and arrhythmias).
- To prevent hypokalemia, instruct patients (especially those predisposed to hypokalemia due to long-term diuretic therapy) to include in their diet foods rich in potassium—oranges, bananas,

tomatoes, milk, dried fruits, apricots, peanuts and dark green, leafy vegetables.

ALERT

Monitor the patient's cardiac rhythm and respond to any irregularities immediately.

For hyperkalemia:

- As in hypokalemia, frequently monitor serum potassium and other electrolyte levels, and carefully record intake and output.
- Administer sodium polystyrene sulfonate orally or rectally (by retention enema) in patients with significant potassium elevations because of intravascular sodium shifting. Watch for signs of hypokalemia with prolonged use and for clinical effects of hypoglycemia (muscle weakness, syncope, hunger, diaphoresis) with repeated insulin and glucose treatment.
- Watch for signs of hyperkalemia in predisposed patients, especially those with poor urine output or those receiving potassium supplements orally or I.V. Administer no more than 10 to 20 mEq/L of potassium chloride per hour; check the I.V. infusion site for signs of phlebitis or infiltration of potassium into tissues. Also, before giving a blood transfusion, check to see how long ago the blood was donated; cell hemolysis in older blood releases potassium. Infuse only *fresh* blood for patients with average to high serum potassium levels.
- Watch for and report cardiac arrhythmias.

Sodium imbalance

Sodium is the major cation (90%) in extracellular fluid (ECF); potassium, the major cation in intracellular fluid. During repolarization, the sodium-potassium pump continually shifts sodium into the cells and potassium out of the cells; during depolarization, it does the reverse. Sodium cation functions include maintaining tonicity and concentration of ECF, acid-base balance (reabsorption of sodium ion and excretion of hydrogen ion), nerve conduction and neuromuscular function, glandular secretion, and water balance. Although the body requires only 2 to 4 g of sodium daily, most Americans consume 6 to 10 g daily (mostly sodium

chloride, as table salt), excreting excess sodium through the kidneys and skin.

A low-sodium diet or excessive use of diuretics may induce hyponatremia (decreased serum sodium concentration); dehydration may induce hypernatremia (increased serum sodium concentration).

Causes and incidence

Hyponatremia can result from:

- excessive GI loss of water and electrolytes due to vomiting, suctioning, or diarrhea; excessive perspiration or fever; use of potent diuretics; or tap-water enemas (When such losses decrease circulating fluid volume, increased secretion of antidiuretic hormone [ADH] promotes maximum water reabsorption, which further dilutes serum sodium. These factors are especially likely to cause hyponatremia when combined with excessive intake of free water.)
- excessive drinking of water, infusion of I.V. dextrose in water without other solutes, malnutrition or starvation, or a low-sodium diet, usually in combination with one of the other causes
- trauma, surgery (wound drainage), or burns, which cause sodium to shift into damaged cells

CLINICAL EFFECTS OF SODIUM IMBALANCE

Dysfunction	Hyponatremia	Hypernatremia
Cardiovascular	▪ Hypotension; tachycardia; with severe deficit, vasomotor collapse, thready pulse	▪ Hypertension, tachycardia, pitting edema, excessive weight gain
Cutaneous	▪ Cold, clammy skin; decreased skin turgor	▪ Flushed skin; dry, sticky mucous membranes
Gastrointestinal	▪ Nausea, vomiting, abdominal cramps	▪ Rough, dry tongue; intense thirst
Genitourinary	▪ Oliguria or anuria	▪ Oliguria

Neurologic	▪ Anxiety, headaches, muscle twitching and weakness, seizures	▪ Fever, agitation, restlessness, seizures
Respiratory	▪ Cyanosis with severe deficiency	▪ Dyspnea, respiratory arrest, and death (from dramatic rise in osmotic pressure)

- adrenal gland insufficiency (Addison's disease) or hypoaldosteronism
- cirrhosis of the liver with ascites
- syndrome of inappropriate antidiuretic hormone (SIADH), resulting from brain tumor, stroke, pulmonary disease, or neoplasm with ectopic ADH production. Certain drugs, such as chlorpropamide and clofibrate, may produce a SIADH-like syndrome.

Causes of hypernatremia include:

- decreased water intake (When severe vomiting and diarrhea cause water loss that exceeds sodium loss, serum sodium levels rise, but overall extracellular fluid volume decreases.)
- excess adrenocortical hormones, as in Cushing's syndrome
- ADH deficiency (diabetes insipidus)
- salt intoxication (less common), which may be produced by excessive ingestion of table salt.

Complications

- Seizures
- Coma
- Permanent neurologic damage

Signs and symptoms

Sodium imbalance has profound physiologic effects and can induce severe central nervous system, cardiovascular, and GI abnormalities. For example, hyponatremia may cause renal dysfunction or, if serum sodium loss is abrupt or severe, seizures; hypernatremia may produce

pulmonary edema, circulatory disorders, and decreased level of consciousness. (See *Clinical effects of sodium imbalance*.)

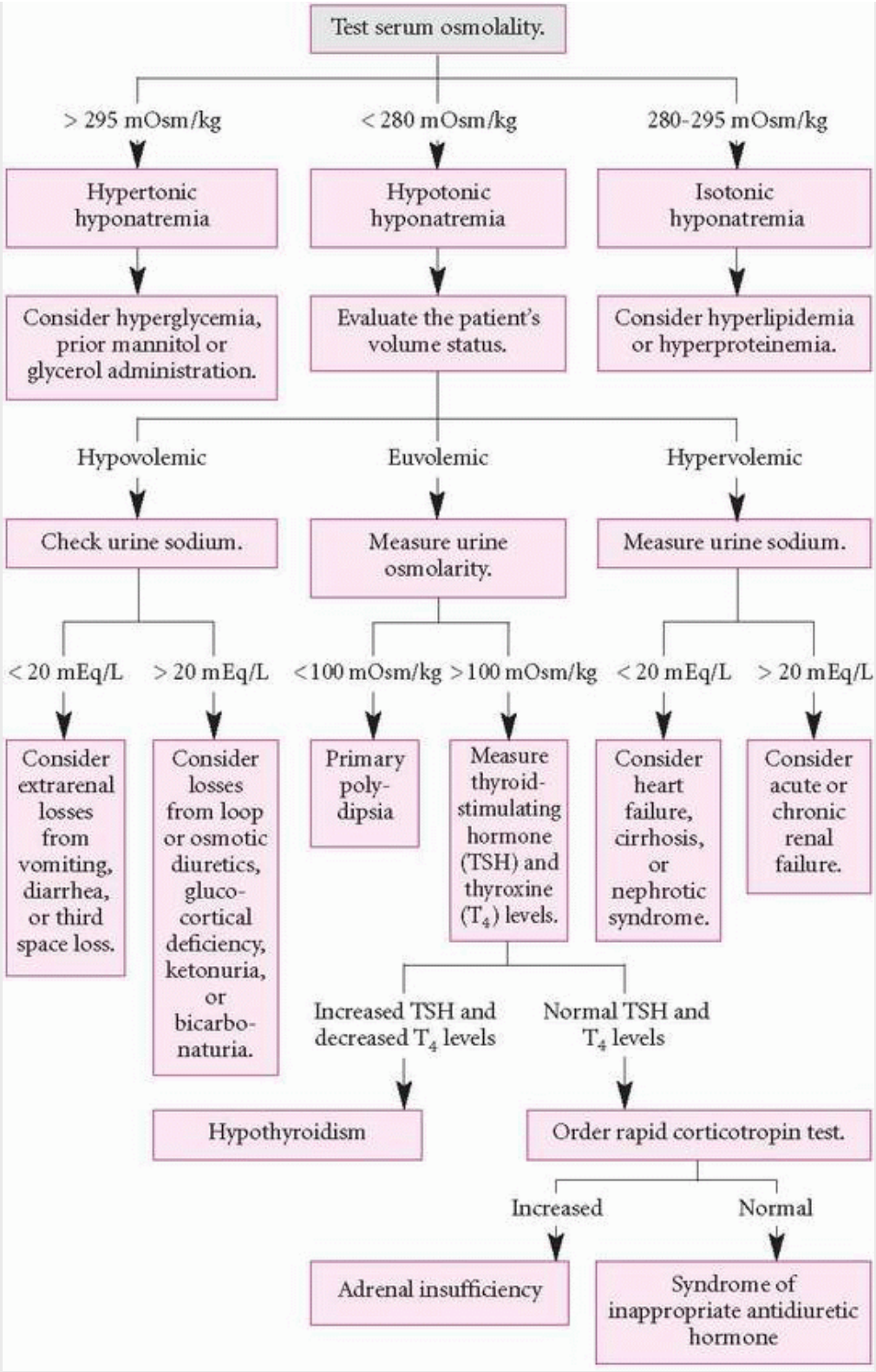
Diagnosis

Hyponatremia is defined as a serum sodium level less than 135 mEq/L; hypernatremia, as a serum sodium level greater than 145 mEq/L. However, additional laboratory studies are necessary to determine etiology and to differentiate between a true deficit and an apparent deficit due to sodium shift or to hypervolemia or hypovolemia. In true hyponatremia, supportive values include urine sodium greater than 100 mEq/24 hours, with low serum osmolality; in true hypernatremia, urine sodium level is less than 40 mEq/24 hours, with high serum osmolality. (See *Diagnosing hyponatremia*.)

DIFFERENTIAL DIAGNOSIS

DIAGNOSING HYPONATREMIA

This flowchart lists possible diagnostic findings and interpretations to assist in treating a patient with hyponatremia.


Test serum osmolality.
> 295 mOsm/kg
< 280 mOsm/kg
280-295 mOsm/kg
Hypertonic hyponatremia
Hypotonic hyponatremia
Isotonic hyponatremia
Consider hyperglycemia, prior mannitol or glycerol administration.
Evaluate the patient's volume status.
Consider hyperlipidemia or hyperproteinemia.
Hypovolemic
Euvolemic
Hypervolemic
Check urine sodium.
Measure urine osmolarity.
Measure urine sodium.
< 20 mEq/L
> 20 mEq/L
<100 mOsm/kg
>100 mOsm/kg
< 20 mEq/L
> 20 mEq/L
Consider extrarenal losses from vomiting, diarrhea, or third space loss.
Consider losses from loop or osmotic diuretics, gluco-cortical deficiency, ketonuria, or bicarbo-naturia.
Primary poly-dipsia
Measure thyroid-stimulating hormone (TSH) and thyroxine (T_4) levels.
Consider heart failure, cirrhosis, or nephrotic syndrome.
Consider acute or chronic renal failure.
Increased TSH and decreased T_4 levels
Normal TSH and T_4 levels
Hypothyroidism
Order rapid corticotropin test.
Increased
Normal
Adrenal insufficiency
Syndrome of inappropriate antidiuretic hormone

Treatment

Therapy for mild hyponatremia usually consists of restricted free-water intake when it's due to hemodilution, SIADH, or such conditions as heart failure, cirrhosis of the liver, and renal failure. If fluid restriction alone fails to normalize serum sodium levels, demeclocycline or lithium, which blocks ADH action in the renal tubules, can be used to promote water excretion. In extremely rare instances of severe symptomatic hyponatremia, when serum sodium levels fall below 110 mEq/L, treatment may include infusion of 3% or 5% saline solution.

Treatment with saline infusion requires careful monitoring of venous pressure to prevent potentially fatal circulatory overload. The aim of treatment of secondary hyponatremia is to correct the underlying disorder.

Primary treatment of hypernatremia is administration of salt-free solutions (such as dextrose in water) to return serum sodium levels to normal, followed by infusion of half-normal saline solution to prevent hyponatremia. Other measures include a sodium-restricted diet and discontinuation of drugs that promote sodium retention.

Special considerations

When managing the patient with hyponatremia:

- Watch for and report extremely low serum sodium and accompanying serum chloride levels. Monitor urine specific gravity and other laboratory results. Record fluid intake and output accurately, and weigh the patient daily.
- During administration of isosmolar or hyperosmolar saline solution, watch closely for signs of hypervolemia (dyspnea, crackles, engorged jugular or hand veins). Report conditions that may cause excessive sodium loss (diaphoresis or prolonged diarrhea or vomiting, and severe burns).
- Refer the patient on maintenance dosage of diuretics to a dietitian for instruction about dietary sodium intake.

PREVENTION

To prevent hyponatremia, administer isosmolar solutions.

When managing the patient with hypernatremia:

- Measure serum sodium levels at least every 6 hours until stabilized. Monitor vital signs for changes, especially for rising pulse rate. Watch for signs of hypervolemia, especially in the patient receiving I.V. fluids.
- Record fluid intake and output accurately, checking for body fluid loss. Weigh the patient daily.
- Obtain a drug history to check for drugs that promote sodium retention.
- Explain the importance of sodium restriction and teach the patient how to plan a low-sodium diet. Closely monitor the serum sodium levels of high-risk patients.

Calcium imbalance

Calcium plays an indispensable role in cell permeability, bone and teeth formation, blood coagulation, transmission of nerve impulses, and normal muscle contraction. Nearly all (99%) of the body's calcium is found in the bones. The remaining 1% exists in the blood, with 50% of the remainder bound to plasma proteins and 40% ionized or free. The ionized calcium in the serum is critical to healthy neurologic function. The parathyroid glands regulate ionized calcium and determine its resorption into bone, absorption from the GI mucosa, and excretion in urine and feces. Severe calcium imbalance requires emergency treatment because a deficiency (hypocalcemia) can lead to tetany and seizures; an excess (hypercalcemia), to cardiac arrhythmias and coma. (See *Clinical effects of calcium imbalance*.)

Causes and incidence

Common causes of hypocalcemia include:

- inadequate intake of calcium and vitamin D, in which inadequate levels of vitamin D inhibit intestinal absorption of calcium

- hypoparathyroidism as a result of injury, disease, or surgery that decreases or eliminates secretion of parathyroid hormone (PTH), which is needed for calcium absorption and normal serum calcium levels
- malabsorption or loss of calcium from the GI tract, caused by increased intestinal motility from severe diarrhea or laxative abuse; can also result from inadequate levels

  of vitamin D or PTH, or a reduction in gastric acidity, decreasing the solubility of calcium salts

CLINICAL EFFECTS OF CALCIUM IMBALANCE

Dysfunction	Hypocalcemia	Hypercalcemia
Cardiovascular	▪ Arrhythmias, hypotension	▪ Signs of heart block, cardiac arrest in systole, hypertension
Gastrointestinal	▪ Increased GI motility, diarrhea	▪ Anorexia, nausea, vomiting, constipation, dehydration, polydipsia
Musculoskeletal	▪ Paresthesia (tingling and numbness of the fingers), tetany or painful tonic muscle spasms, facial spasms, abdominal cramps, muscle cramps, spasmodic contractions	▪ Weakness, muscle flaccidity, bone pain, pathologic fractures
Neurologic	▪ Anxiety, irritability, twitching around mouth, laryngospasm, seizures, Chvostek's sign, Trousseau's sign	▪ Drowsiness, lethargy, headaches, depression or apathy, irritability, confusion
Other	▪ Blood-clotting abnormalities	▪ Renal polyuria, flank pain and, eventually, azotemia

- severe infections or burns, in which diseased and burned tissue traps calcium from the extracellular fluid
- overcorrection of acidosis, resulting in alkalosis, which causes decreased ionized calcium and induces symptoms of hypocalcemia
- pancreatic insufficiency, which may cause malabsorption of calcium and subsequent calcium loss in feces. In pancreatitis, participation of calcium ions in saponification contributes to calcium loss
- renal failure, resulting in excessive excretion of calcium secondary to increased retention of phosphate
- hypomagnesemia, which causes decreased PTH secretion and blocks the peripheral action of that hormone.

Causes of hypercalcemia include the following:

- hyperparathyroidism, which increases serum calcium levels by promoting calcium absorption from the intestine, resorption from bone, and reabsorption from the kidneys
- hypervitaminosis D, which can promote increased absorption of calcium from the intestine
- tumors, which raise serum calcium levels by destroying bone or by releasing PTH or a PTH-like substance, osteoclastactivating factor, prostaglandins and, perhaps, a vitamin D-like sterol
- multiple fractures and prolonged immobilization, which release bone calcium and raise the serum calcium level
- multiple myeloma, which promotes loss of calcium from bone.

Other causes include milk-alkali syndrome, sarcoidosis, hyperthyroidism, adrenal insufficiency, thiazide diuretics, and loss of serum albumin secondary to renal disease.

Complications

- Laryngeal spasm, tetany, seizures and possibly respiratory arrest (hypocalcemia)
- coma and cardiac arrest (hypercalcemia)

TROUSSEAU'S SIGN

To check for Trousseau's sign, apply a blood pressure cuff to the patient's arm. A carpopedal spasm that causes thumb adduction and phalangeal extension, as shown, confirms tetany.

Signs and symptoms

Calcium deficit causes nerve fiber irritability and repetitive muscle spasms. Consequently, characteristic symptoms of hypocalcemia include perioral paresthesia, twitching, carpopedal spasm, tetany, seizures and, possibly, cardiac arrhythmias. Chvostek's sign and Trousseau's sign are reliable indicators of hypocalcemia. (See *Trousseau's sign*. Also see *Chvostek's sign.*)

Clinical effects of hypercalcemia include muscle weakness, decreased muscle tone, lethargy, anorexia, constipation, nausea, vomiting, dehydration, polydipsia, and polyuria. Severe hypercalcemia (serum levels that exceed 15 mg/dl) may produce cardiac arrhythmias and, eventually, coma.

Diagnosis

CONFIRMING DIAGNOSIS

A serum calcium level less than 8.5 mg/ dl confirms hypocalcemia; a level more than 10.5 mg/dl confirms hypercalcemia. (However, because approximately one-half of serum calcium is bound to albumin, changes in serum protein must be considered when interpreting serum calcium levels. A common conversion formula is calcium corrected = calcium actual + 0.8 × [4.0 - albumin level]. Ionized calcium levels are 4.65 to 5.28 mg/dl and are a measure of the fraction of serum calcium in ionized form.)

The Sulkowitch urine test shows increased calcium precipitation in hypercalcemia. In hypocalcemia, an electrocardiogram (ECG) reveals lengthened QT interval, prolonged ST segment, and arrhythmias; in hypercalcemia, shortened QT interval and heart block. (See *Diagnosing hypercalcemia,* pages 590 and 591.)

Treatment

Treatment varies and requires correction of the acute imbalance, followed by maintenance therapy and correction of the underlying cause. Mild hypocalcemia may require nothing more than an adjustment in diet to allow adequate intake of calcium, vitamin D, and protein, possibly with oral calcium supplements. Acute hypocalcemia is an emergency that needs immediate correction by I.V. administration of calcium gluconate or calcium chloride. Chronic hypocalcemia also requires vitamin D supplements to facilitate GI absorption of calcium. To correct mild deficiency states, the amounts of vitamin D in most multivitamin preparations are adequate. For severe deficiency, vitamin D is used in four forms: ergocalciferol (vitamin D_2), cholecalciferol (vitamin D_3), calcitriol, and dihydrotachysterol, a synthetic form of vitamin D_2.

Treatment of hypercalcemia primarily eliminates excess serum calcium through hydration with normal saline solution, which promotes calcium excretion in the urine. Loop diuretics, such as ethacrynic acid and

furosemide, also promote calcium excretion. (Thiazide diuretics are contraindicated in hypercalcemia because they inhibit calcium excretion.) Corticosteroids, such as prednisone and hydrocortisone, are helpful in treating sarcoidosis, hypervitaminosis D, and certain tumors. Plicamycin can also lower serum calcium levels and is especially effective against hypercalcemia secondary to certain tumors. Calcitonin may also be helpful in certain instances.

Sodium phosphate solution administered orally or by retention enema promotes calcium deposition in bone and inhibits its absorption from the GI tract.

Special considerations

Watch for hypocalcemia in patients receiving massive transfusions of citrated blood; in those with chronic diarrhea, severe infections, and insufficient dietary intake of calcium and protein (especially in elderly patients); and in those who are hyperventilating.

- Check serum calcium level every 12 to 24 hours, and report a calcium level less than 8.5 mg/dl immediately. When giving calcium supplements, frequently check the pH level because a pH lower than 7.45 inhibits calcium ionization. Check for Trousseau's and Chvostek's signs.
- Administer calcium gluconate slow I.V. in 5% dextrose in water (*never* in saline solution, which encourages renal calcium loss). Don't add calcium gluconate I.V. to solutions containing bicarbonate; it will precipitate. When administering calcium solutions, watch for anorexia, nausea, and vomiting—possible signs of overcorrection to hypercalcemia. Never infuse more than 1g/hour, except in an emergency. Use a volume-control device to ensure proper flow rate.
- If the patient is receiving calcium chloride, watch for abdominal discomfort.

ALERT

Don't confuse calcium chloride with calcium gluconate in administration; 1 gm of calcium chloride has three times the calcium as 1 gm of calcium gluconate.

- Monitor the patient closely for a possible drug interaction if he's receiving cardiac glycosides with large doses of oral calcium supplements; watch for signs of digoxin toxicity (anorexia, nausea, vomiting, yellow vision, and cardiac arrhythmias). Administer oral calcium supplements 1 to 11/2 hours after meals or with milk.
- Provide a quiet, stress-free environment for the patient with tetany. Observe seizure precautions for patients with severe hypocalcemia.

PREVENTION

To prevent hypocalcemia, advise all patients—especially elderly patients—to eat foods rich in calcium, vitamin D, and protein, such as fortified milk and cheese. Explain how important calcium is for normal bone formation and blood coagulation. Discourage chronic use of laxatives. Also, warn hypocalcemic patients not to overuse antacids, because these may aggravate the condition.

CHVOSTEK'S SIGN

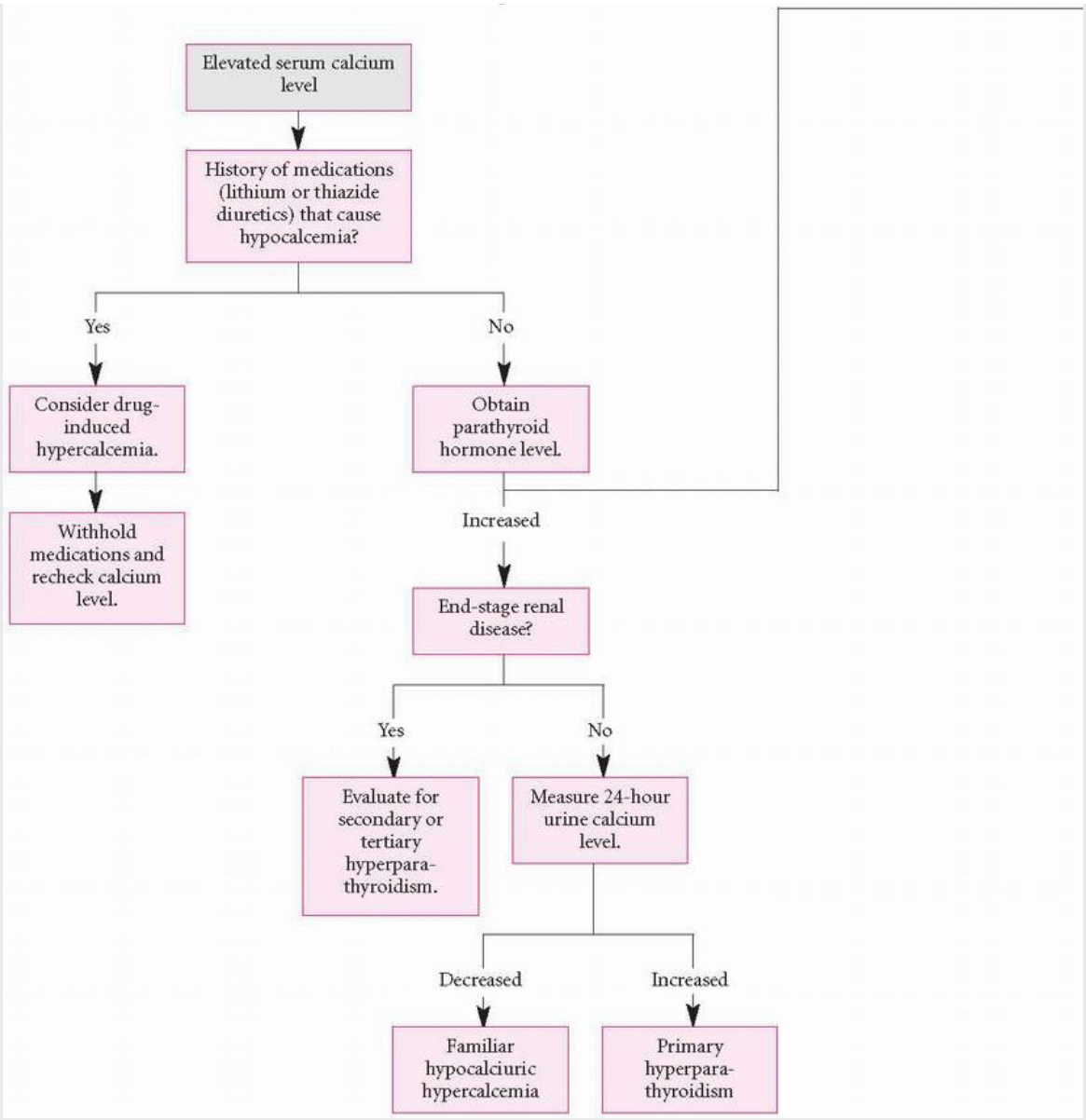
To check for Chvostek's sign, tap the facial nerve above the mandibular angle, adjacent to the earlobe. A facial muscle spasm that causes the patient's upper lip to twitch, as shown, confirms tetany.

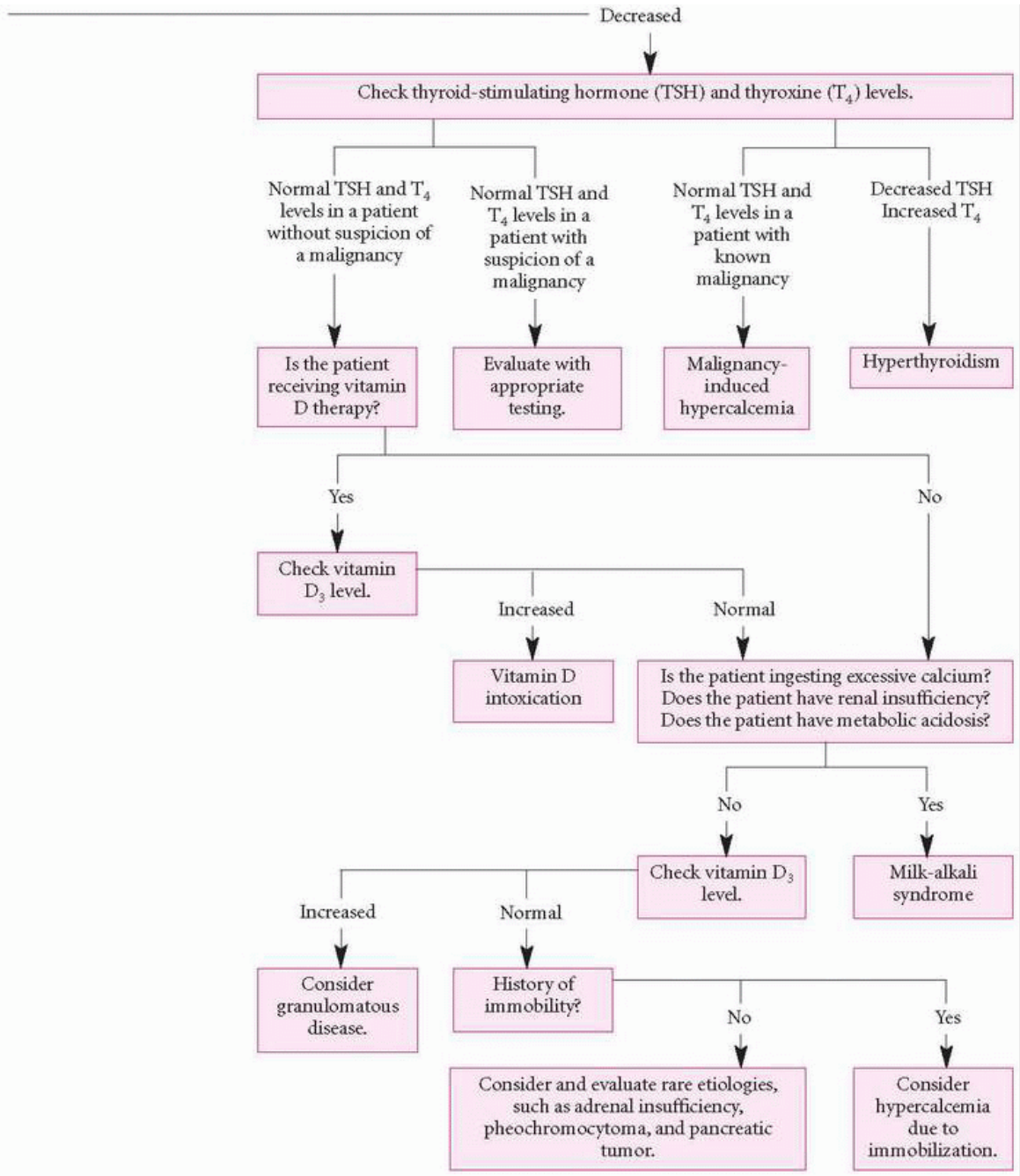
If the patient has hypercalcemia:

- Check serum calcium level frequently. Watch for cardiac arrhythmias if serum calcium levels exceed their normal values of 8.5 to 10.5 mg/dl. Increase fluid intake to dilute calcium in serum and urine, and to prevent renal damage and dehydration. Watch for signs of heart failure in patients receiving normal saline diuresis.
- Administer loop diuretics (not thiazide diuretics), as ordered. Monitor intake and output, and check urine for renal calculi and acidity. Provide acid-ash drinks, such as cranberry or prune juice, because calcium salts are more soluble in acid than in alkali.

DIFFERENTIAL DIAGNOSIS
DIAGNOSING HYPERCALCEMIA

This flowchart lists possible diagnostic findings and interpretations to assist with treatment of the patient with hypercalcemia.


Elevated serum calcium level
History of medications (lithium or thiazide diuretics) that cause hypocalcemia?
Yes
No
Consider drug-induced hypercalcemia.
Withhold medications and recheck calcium level.
Obtain parathyroid hormone level.
Increased
End-stage renal disease?
Yes
No
Evaluate for secondary or tertiary hyperpara-thyroidism.
Measure 24-hour urine calcium level.
Decreased
Increased
Familiar hypocalciuric hypercalcemia
Primary hyperpara-thyroidism



- Check ECG and vital signs frequently. In the patient receiving cardiac glycosides, watch for signs of toxicity, such as anorexia, nausea, vomiting, and bradycardia (often with arrhythmia).

- Ambulate the patient as soon as possible. Handle the patient with chronic hypercalcemia *gently* to prevent pathologic fractures. If the patient is bedridden, reposition him frequently and encourage range-of-motion exercises to promote circulation and prevent urinary stasis and calcium loss from bone.
- To prevent recurrence, suggest a lowcalcium diet, with increased fluid intake.

Chloride imbalance

Hypochloremia and hyperchloremia are, respectively, conditions of deficient or excessive serum levels of the chloride anion. A predominantly extracellular anion, chloride accounts for two-thirds of all serum anions. Secreted by stomach mucosa as hydrochloric acid, it provides an acid medium that aids digestion and activation of enzymes. Chloride also participates in maintaining acid-base and body water balances, influences the osmolality or tonicity of extracellular fluid (ECF), plays a role in the exchange of oxygen and carbon dioxide in red blood cells, and helps activate salivary amylase (which, in turn, activates the digestive process).

Causes and incidence

Hypochloremia may result from:

- decreased chloride intake or absorption, as in low dietary sodium intake, sodium deficiency, potassium deficiency, metabolic alkalosis; prolonged use of mercurial diuretics; or administration of dextrose I.V. without electrolytes
- excessive chloride loss resulting from prolonged diarrhea or diaphoresis; loss of hydrochloric acid in gastric secretions due to vomiting, gastric suctioning, or gastric surgery.

Hyperchloremia may result from:

- excessive chloride intake or absorption —as in hyperingestion of ammonium chloride, or ureterointestinal anastomosis —allowing

reabsorption of chloride by the bowel

- hemoconcentration from dehydration
- compensatory mechanisms for other metabolic abnormalities, as in metabolic acidosis, brain stem injury causing neurogenic hyperventilation, and hyperparathyroidism.

Complications

- Depressed respirations leading to respiratory arrest (hypochloremia)
- Coma (hyperchloremia)

Signs and symptoms

Hypochloremia is usually associated with hyponatremia and its characteristic muscle weakness and twitching because renal chloride loss always accompanies sodium loss, and sodium reabsorption isn't possible without chloride. However, if chloride depletion results from metabolic alkalosis secondary to loss of gastric secretions, chloride is lost independently from sodium; typical symptoms are muscle hypertonicity, tetany, and shallow, depressed breathing.

Because of the natural affinity of sodium and chloride ions, hyperchloremia usually produces clinical effects associated with hypernatremia and resulting ECF volume excess (agitation, tachycardia, hypertension, pitting edema, dyspnea). Hyperchloremia associated with metabolic acidosis is due to excretion of base bicarbonate by the kidneys, and induces deep, rapid breathing; weakness; diminished cognitive ability; and, ultimately, coma.

Diagnosis

CONFIRMING DIAGNOSIS

A serum chloride level below 98 mEq/L confirms hypochloremia. (Supportive values in metabolic alkalosis include serum pH above 7.45 and serum carbon dioxide [CO_2] level above 32 mEq/L.) A serum chloride level above 108 mEq/L confirms hyperchloremia; with

metabolic acidosis, serum pH is below 7.35 and serum CO_2 level is below 22 mEq/L.

Treatment

Hypochloremia therapy aims to correct the condition that causes excessive chloride

loss and to give oral replacement such as salty broth. When oral therapy isn't possible, or when emergency measures are necessary, treatment may include normal saline solution I.V. (if hypovolemia is present) or chloride-containing drugs, such as ammonium chloride, to increase serum chloride levels, and potassium chloride for metabolic alkalosis. For severe hyperchloremic acidosis, treatment consists of sodium bicarbonate I.V. to raise the serum bicarbonate level and permit renal excretion of the chloride anion, because bicarbonate and chloride compete for combination with sodium. For mild hyperchloremia, Ringer's lactate solution is administered; it converts to bicarbonate in the liver, thus increasing base bicarbonate to correct acidosis.

In either kind of chloride imbalance, treatment must correct the underlying disorder.

Special considerations

When managing the patient with hypochloremia:

- Check serum chloride level frequently, particularly during I.V. therapy.
- Watch for signs of hyperchloremia or hypochloremia. Be alert for respiratory difficulty.
- To prevent hypochloremia, monitor laboratory results (serum electrolyte levels and blood gas values) and fluid intake and output of patients who are vulnerable to chloride imbalance, particularly those recovering from gastric surgery. Record and report excessive or continuous loss of gastric secretions. Also report prolonged infusion of dextrose in water without saline.

When managing the patient with hyperchloremia:

- Check serum electrolyte levels every 3 to 6 hours. If the patient is receiving high doses of sodium bicarbonate, watch for signs of overcorrection (metabolic alkalosis, respiratory depression) or lingering signs of hyperchloremia, which indicate inadequate treatment.

PREVENTION

To prevent hyperchloremia, check laboratory results for elevated serum chloride levels or potassium imbalance if the patient is receiving I.V. solutions containing sodium chloride, and monitor fluid intake and output. Also, watch for signs of metabolic acidosis. When administering I.V. fluids containing Ringer's lactate solution, monitor flow rate according to the patient's age, physical condition, and bicarbonate level. Report any irregularities promptly.

Magnesium imbalance

Magnesium is the second most common cation in intracellular fluid. Although its major function is to enhance neuromuscular integration, it also stimulates parathyroid hormone (PTH) secretion, thus regulating intracellular fluid calcium levels. Therefore, magnesium deficiency (hypomagnesemia) may result in transient hypoparathyroidism or interference with the peripheral action of PTH. Magnesium may also regulate skeletal muscles through its influence on calcium utilization by depressing acetylcholine release at synaptic junctions. In addition, magnesium activates many enzymes for proper carbohydrate and protein metabolism, aids in cell metabolism and the transport of sodium and potassium across cell membranes, and influences sodium, potassium, calcium, and protein levels.

About one-third of magnesium taken into the body is absorbed through the small intestine and is eventually excreted in the urine; the remaining unabsorbed magnesium is excreted in the stool.

Because many common foods contain magnesium, a dietary deficiency is rare. Hypomagnesemia generally follows impaired absorption, too-rapid excretion, or inadequate intake during total parenteral nutrition. It frequently coexists with other electrolyte imbalances, especially low

calcium and potassium levels. Magnesium excess (hypermagnesemia) is common in patients with renal failure and excessive intake of magnesium-containing antacids.

Causes and incidence

Hypomagnesemia usually results from impaired absorption of magnesium in the intestines or excessive excretion in urine or stool. Possible causes include:

- decreased magnesium intake or absorption, as in malabsorption syndrome,

  chronic diarrhea, or postoperative complications after bowel resection; chronic alcoholism; prolonged diuretic therapy, nasogastric suctioning, or administration of parenteral fluids without magnesium salts; and starvation or malnutrition
- excessive loss of magnesium, as in severe dehydration and diabetic acidosis; hyperaldosteronism and hypoparathyroidism, which result in hypokalemia and hypocalcemia; hyperparathyroidism and hypercalcemia; excessive release of adrenocortical hormones; and diuretic therapy.

Hypermagnesemia results from the kidneys' inability to excrete magnesium that was either absorbed from the intestines or infused. Common causes of hypermagnesemia include:

- chronic renal insufficiency
- use of laxatives (magnesium sulfate, milk of magnesia, and magnesium citrate solutions), especially with renal insufficiency
- overuse of magnesium-containing antacids
- severe dehydration (resulting oliguria can cause magnesium retention)
- overcorrection of hypomagnesemia.

Complications

- Cardiac arrhythmias, hypoparathyroidism, seizures, confusion and coma (hypomagnesemia)

- Complete heart block and respiratory paralysis (hypermagnesemia)

Signs and symptoms

Hypomagnesemia causes neuromuscular irritability and cardiac arrhythmias. Hypermagnesemia causes central nervous system and respiratory depression, in addition to neuromuscular and cardiac effects. (See *Signs and symptoms of magnesium imbalance*.)

Diagnosis

CONFIRMING DIAGNOSIS

Serum magnesium level less than 1.5 mEq/ L confirms hypomagnesemia; a level greater than 2.5 mEq/L confirms hypermagnesemia.

Low levels of other serum electrolytes (especially potassium and calcium) often coexist with hypomagnesemia. In fact, unresponsiveness to correct treatment for hypokalemia strongly suggests hypomagnesemia. Similarly, elevated levels of other serum electrolytes are associated with hypermagnesemia.

Treatment

Therapy for magnesium imbalance aims to identify and correct the underlying cause.

Treatment of mild hypomagnesemia consists of daily magnesium supplements I.M. or orally; of severe hypomagnesemia, magnesium sulfate I.V. (10 to 40 mEq/L diluted in I.V. fluid). Magnesium intoxication (a possible adverse effect) requires calcium gluconate I.V.

Therapy for hypermagnesemia includes increased fluid intake and loop diuretics (such as furosemide) with impaired renal function; calcium gluconate (10%), a magnesium antagonist, for temporary relief of symptoms in an emergency; and peritoneal dialysis or hemodialysis if renal function fails or if excess magnesium can't be eliminated.

Special considerations

For patients with hypomagnesemia:

- Monitor serum electrolyte levels (including magnesium, calcium, and potassium) daily for mild deficits and every 6 to 12 hours during replacement therapy.
- Measure intake and output frequently. (Urine output shouldn't fall below 0.5 to 1 ml/kg/day in patients with healthy body weight; in heavier patients, less than 50 ml/hour is a cause for concern.) Remember, the kidneys excrete excess magnesium, and hypermagnesemia could occur with renal insufficiency.

ALERT

Monitor vital signs during I.V. therapy. Infuse magnesium replacement slowly and watch for bradycardia, heart block, and decreased respiratory rate. Have calcium gluconate I.V. available to reverse hypermagnesemia from overcorrection. In patients with torsade de pointes, elevated magnesium levels are therapeutic.

- Advise patients to eat foods high in magnesium, such as fish and green vegetables.
- Watch for and report signs of hypomagnesemia in patients with predisposing diseases or conditions, especially those not permitted anything by mouth or who receive I.V. fluids without magnesium.

SIGNS AND SYMPTOMS OF MAGNESIUM IMBALANCE

Dysfunction	Hypomagnesemia	Hypermagnesemia
Cardiovascular	▪ Arrhythmias (such as torsade de pointes), vasomotor changes (vasodilation and hypotension) and, occasionally, hypertension	▪ Bradycardia, weak pulse, hypotension, heart block, cardiac arrest (common with serum levels of 25 mEq/L)

Neurologic	▪ Confusion, delusions, hallucinations, seizures	▪ Drowsiness, flushing, lethargy, confusion, diminished sensorium
Neuromuscular	▪ Hyperirritability, tetany, leg and foot cramps, Chvostek's sign (facial muscle spasms induced by tapping the branches of the facial nerve)	▪ Diminished reflexes, muscle weakness, flaccid paralysis, respiratory muscle paralysis that may cause respiratory insufficiency

For patients with hypermagnesemia:

- Frequently assess level of consciousness, muscle activity, and vital signs.
- Keep accurate intake and output records. Provide sufficient fluids for adequate hydration and maintenance of renal function.
- Report abnormal serum electrolyte levels immediately.
- Monitor and report electrocardiogram changes (peaked T waves, increased PR intervals, widened QRS complex).
- Watch patients receiving cardiac glycosides and calcium gluconate simultaneously, because calcium excess enhances digoxin action, predisposing the patient to digoxin toxicity.
- Advise patients, particularly elderly patients and patients with compromised renal function, not to abuse laxatives and antacids containing magnesium.
- Watch for signs of hypermagnesemia in predisposed patients. Observe closely for respiratory distress if magnesium serum levels rise above 10 mEq/L.

Phosphorus imbalance

Phosphorus exists primarily in inorganic combination with calcium in teeth and bones. In extracellular fluid, the phosphate ion supports several metabolic functions: utilization of B vitamins, acid-base homeostasis, bone formation, nerve and muscle activity, cell division, transmission of hereditary traits, and metabolism of carbohydrates, proteins, and fats. Renal tubular reabsorption of phosphate is inversely regulated by calcium levels—an increase in phosphorus causes a

decrease in calcium. An imbalance causes hypophosphatemia or hyperphosphatemia. Incidence of hypophosphatemia varies with the underlying cause; hyperphosphatemia occurs most often in children, who tend to consume more phosphorus-rich foods and beverages than adults, and in children and adults with renal insufficiency. The prognosis for both conditions depends on the underlying cause.

Causes and incidence

Hypophosphatemia is usually the result of inadequate dietary intake; it's often related to malnutrition resulting from a prolonged catabolic state or chronic alcoholism. It may also stem from intestinal malabsorption, chronic diarrhea, hyperparathyroidism with resultant hypercalcemia, hypomagnesemia, or deficiency of vitamin D, which is necessary for intestinal phosphorus absorption. Other causes include chronic use of antacids containing aluminum hydroxide, use of parenteral nutrition solution with inadequate phosphate content, renal tubular defects, tissue damage in which phosphorus is released by injured cells, and diabetic acidosis.

FOODS HIGH IN PHOSPHORUS

Food	Portion	Amount (mg)
Almonds	2/3 cup	475
Beef liver (fried)	31/2 oz	476
Broccoli (cooked)	2/3 cup	62
Carbonated beverages	12 oz	Up to 500
Milk (whole)	8 oz	93
Turkey (roasted)	31/2 oz	251

Hyperphosphatemia is generally secondary to hypocalcemia, hypervitaminosis D, hypoparathyroidism, or renal failure (often due to

stress or injury). It may also result from overuse of laxatives with phosphates or phosphate enemas.

Complications

- *Hypophosphatemia* — heart failure, shock, arrhythmias, rhabdomyolysis, seizures, and coma
- *Hyperphosphatemia* — soft-tissue complications

Signs and symptoms

Hypophosphatemia produces anorexia, muscle weakness, tremor, paresthesia and, when persistent, osteomalacia, causing bone pain. Impaired red blood cell functions may occur in hypophosphatemia due to alterations in oxyhemoglobin dissociation, which may result in peripheral hypoxia. Hyperphosphatemia usually remains asymptomatic unless it results in hypocalcemia, with tetany and seizures.

Diagnosis

CONFIRMING DIAGNOSIS

Serum phosphorus levels less than 1.7 mEq/ L or 2.5 mg/dl confirm hypophosphatemia. Urine phosphorus levels above 1.3 g/24 hours support this diagnosis. Serum phosphorus levels above 2.6 mEq/L or 4.5 mg/dl confirm hyperphosphatemia. Supportive values include decreased levels of serum calcium (less than 9 mg/dl) and urine phosphorus (less than 0.9 g/24 hours).

Treatment

Treatment aims to correct the underlying cause of phosphorus imbalance. Until this is done, management of hypophosphatemia consists of phosphorus replacement with a high-phosphorus diet and oral administration of phosphate salt tablets or capsules. (See *Foods high in phosphorus*.) Severe hypophosphatemia requires I.V. infusion of

potassium phosphate. Severe hyperphosphatemia may require peritoneal dialysis or hemodialysis to lower the serum phosphorus level.

Special considerations

- Carefully monitor serum electrolyte, calcium, magnesium, and phosphorus levels. Report any changes immediately.

To manage hypophosphatemia:

- Record intake and output accurately. Administer potassium phosphate slow I.V. to prevent overcorrection to hyperphosphatemia. Assess renal function and be alert for hypocalcemia when giving phosphate supplements. If phosphate salt tablets cause nausea, use capsules instead.
- To prevent recurrence, advise the patient to follow a high-phosphorus diet containing milk and milk products, kidney, liver, turkey, and dried fruits.

To manage hyperphosphatemia:

- Monitor intake and output. If urine output falls below 25 ml/hour or 600 ml/day, notify the physician immediately, because decreased output can seriously affect renal clearance of excess serum phosphorus.
- Watch for signs of hypocalcemia, such as muscle twitching and tetany, which often accompany hyperphosphatemia.
- To prevent recurrence, advise the patient to eat foods with low phosphorus content such as vegetables. Obtain dietary consultation if the condition results from chronic renal insufficiency.

Syndrome of inappropriate antidiuretic hormone

Syndrome of inappropriate antidiuretic hormone (SIADH), also known as *dilutional hyponatremia*, is marked by excessive release of antidiuretic hormone (ADH), which disturbs fluid and electrolyte balance. Such disturbances result from the inability to excrete dilute urine, free water retention, extracellular fluid volume expansion, and hyponatremia.

SIADH occurs secondary to diseases that affect the osmoreceptors (supraoptic nucleus) of the hypothalamus. The prognosis depends on the underlying disorder and response to treatment.

Causes and incidence

The most common cause of SIADH (80% of patients) is oat cell carcinoma of the lung, which secretes excessive ADH or vasopressor-like substances. Other neoplastic diseases, such as pancreatic and prostatic cancer, Hodgkin's lymphoma, and thymoma, may also trigger SIADH.

Less common causes include:

- central nervous system disorders: brain tumor or abscess, stroke, head injury, Guillain-Barré syndrome, and lupus erythematosus
- pulmonary disorders: pneumonia, tuberculosis, lung abscess, and positive-pressure ventilation
- drugs: chlorpropamide, vincristine, cyclophosphamide, carbamazepine, clofibrate, and morphine
- miscellaneous conditions: myxedema and psychosis.

Complications

- Water intoxification
- Cerebral edema
- Severe hyponatremia
- Coma

Signs and symptoms

SIADH may produce weight gain despite anorexia, nausea, and vomiting; muscle weakness; restlessness; and, possibly, coma and seizures. Edema is rare unless water overload exceeds 4 L because much of the free water excess is within cellular boundaries.

Diagnosis

A complete medical history revealing positive water balance may suggest SIADH.

CONFIRMING DIAGNOSIS

Serum osmolality less than 280 mOsm/kg of water and a serum sodium level below 123 mEq/L confirm the diagnosis (normal urine osmolality is 11/2 times serum values).

Supportive laboratory values include high urine sodium secretion (more than 20 mEq/L) without diuretics and high urine osmolality. In addition, diagnostic studies show normal renal function and no evidence of dehydration.

Treatment

Treatment for SIADH is symptomatic and begins with restricted water intake (500 to 1,000 ml/day). Some patients who continue to have symptoms are given a high-salt, high-protein diet or urea supplements to enhance water excretion. They may also receive demeclocycline or lithium to help block the renal response to ADH. With severe water intoxication, administration of 200 to 300 ml of 5% saline may be necessary to raise the serum sodium level. When possible, treatment should include correction of the underlying cause of SIADH. If SIADH is due to cancer, success in alleviating water retention may be obtained by surgical resection, irradiation, or chemotherapy.

Special considerations

- Closely monitor and record intake and output, vital signs, and daily weight. Watch for hyponatremia.
- Observe the patient for restlessness, irritability, seizures, heart failure, and unresponsiveness due to hyponatremia and water intoxication.
- To prevent water intoxication, explain to the patient and his family why he must restrict his intake.

Metabolic acidosis

Metabolic acidosis is a physiologic state of excess acid accumulation and deficient base bicarbonate produced by an underlying pathologic disorder. Symptoms result from the body's attempts to correct the acidotic condition through compensatory mechanisms in the lungs, kidneys, and cells. Metabolic acidosis is more prevalent among children, who are vulnerable to acid-base imbalance because their metabolic rates are faster and their ratios of water to total-body weight are lower. Severe or untreated metabolic acidosis can be fatal.

Causes and incidence

Metabolic acidosis usually results from excessive fat burning in the absence of usable carbohydrates. This can be caused by diabetic ketoacidosis, chronic alcoholism, malnutrition, or a low-carbohydrate, highfat diet—all of which produce more keto acids than the metabolic process can handle. Other causes include:

- anaerobic carbohydrate metabolism: a decrease in tissue oxygenation or perfusion (as occurs with pump failure after myocardial infarction, or with pulmonary or hepatic disease, shock, or anemia) forces a shift from aerobic to anaerobic metabolism, causing a corresponding rise in lactic acid level
- renal insufficiency and failure (renal acidosis): underexcretion of metabolized acids or inability to conserve base
- diarrhea and intestinal malabsorption: loss of sodium bicarbonate from the intestines, causing the bicarbonate buffer system to shift to the acidic side. For example, ureteroenterostomy and Crohn's disease can also induce metabolic acidosis.

Less often, metabolic acidosis results from salicylate intoxication (overuse of aspirin), exogenous poisoning, or Addison's disease with an increased excretion of sodium and chloride, and retention of potassium ions.

Complications

- Coma

- Arrhythmias
- Cardiac arrest

Signs and symptoms

In mild acidosis, the underlying disease's symptoms may obscure any direct clinical evidence. Metabolic acidosis typically begins with headache and lethargy, progressing to drowsiness, central nervous system depression, Kussmaul's respirations (as the lungs attempt to compensate by “blowing off” carbon dioxide), stupor and, if the condition is severe and goes untreated, coma and death. Associated GI distress usually produces anorexia, nausea, vomiting, and diarrhea, and may lead to dehydration. Underlying diabetes mellitus may cause fruity breath from catabolism of fats and excretion of accumulated acetone through the lungs.

Diagnosis

CONFIRMING DIAGNOSIS

Arterial pH below 7.35 confirms metabolic acidosis. In severe acidotic states, pH may fall to 7.10, and the partial pressure of arterial carbon dioxide may be normal or below 34 mm Hg as compensatory mechanisms take hold. Bicarbonate may be below 22 mEq/L.

A metabolic panel can help reveal the cause and severity of metabolic acidosis. A complete blood count can be done to help assess possible causes as well. Supportive findings include:

- urine pH: below 4.5 in the absence of renal disease
- serum potassium levels: above 5.5 mEq/ L from chemical buffering
- glucose levels: above 150 mg/dl in diabetes
- serum ketone bodies: elevated levels in diabetes mellitus
- serum osmolarity: increased levels, as in hyperosmolar hyperglycemic nonketotic acidosis or dehydration
- plasma lactic acid: elevated levels in lactic acidosis

- anion gap: greater than 14 mEq/L indicating metabolic acidosis (diabetic ketoacidosis, aspirin overdose, alcohol poisoning). (See *Anion gap*.)

Treatment

In metabolic acidosis, treatment consists of administration of sodium bicarbonate I.V. for severe cases, evaluation and correction of electrolyte imbalances and, ultimately, correction of the underlying cause. For example, in diabetic ketoacidosis, a low-dose continuous I.V. infusion of insulin is recommended.

ANION GAP

The anion gap is the difference between concentrations of serum cations and anions —determined by measuring one cation (sodium) and two anions (chloride and bicarbonate). The normal concentration of sodium is 140 mEq/L; of chloride, 102 mEq/L; and of bicarbonate, 26 mEq/L. Thus, the anion gap between *measured* cations (actually sodium alone) and *measured* anions is about 12 mEq/L (140 minus 128).

Concentrations of potassium, calcium, and magnesium (*unmeasured* cations), or proteins, phosphate, sulfate, and organic acids (*unmeasured* anions) aren't needed to measure the anion gap. Added together, the concentration of unmeasured cations would be about 11 mEq/L; of unmeasured anions, about 23 mEq/L. Thus, the normal anion gap between unmeasured cations and anions is about 12 mEq/L (23 minus 11)—plus or minus 2 mEq/L for normal variation. An anion gap over 14 mEq/L indicates *metabolic acidosis.* It may result from accumulation of excess organic acids or from retention of hydrogen ions, which chemically bond with bicarbonate and decrease bicarbonate levels.

Special considerations

- Keep sodium bicarbonate ampules handy for emergency administration. Monitor vital signs, laboratory results, and level of consciousness frequently because changes can occur rapidly.
- In diabetic acidosis, watch for secondary changes due to hypovolemia, such as decreasing blood pressure.
- Record intake and output accurately to monitor renal function. Watch for signs of excessive serum potassium—weakness, flaccid paralysis, and arrhythmias, possibly leading to cardiac arrest. After treatment, check for overcorrection to hypokalemia.
- Because metabolic acidosis commonly causes vomiting, position the patient to prevent aspiration. Prepare for possible seizures with seizure precautions.
- Provide good oral hygiene. Use sodium bicarbonate washes to neutralize mouth acids, and lubricate the patient's lips with lemon and glycerin swabs as indicated.

PREVENTION

Carefully observe patients receiving I.V. therapy or who have intestinal tubes in place as well as those suffering from shock, hyperthyroidism, hepatic disease, circulatory failure, or dehydration. Teach the patient with diabetes how to routinely test urine for glucose and acetone, and encourage strict adherence to insulin or oral hypoglycemic therapy.

Metabolic alkalosis

A clinical state marked by decreased amounts of acid or increased amounts of base bicarbonate, metabolic alkalosis causes metabolic, respiratory, and renal responses, producing characteristic symptoms (most notably hypoventilation). This condition is always secondary to an underlying cause. With early diagnosis and prompt treatment, prognosis is good; however, untreated metabolic alkalosis may lead to coma and death.

Causes and incidence

Metabolic alkalosis results from loss of acid, retention of base, or renal mechanisms associated with decreased serum levels of potassium and chloride.

Causes of critical acid loss include vomiting, nasogastric (NG) tube drainage or lavage without adequate electrolyte replacement, fistulas, and the use of steroids and certain diuretics (furosemide, thiazides, and ethacrynic acid). Hyperadrenocorticism is another cause of severe acid loss. Cushing's disease, primary hyperaldosteronism, and Bartter's syndrome, for example, all lead to retention of sodium and chloride, and urinary loss of potassium and hydrogen.

Excessive base retention can result from excessive intake of bicarbonate of soda or other antacids (usually for treatment of gastritis or peptic ulcer), excessive intake of absorbable alkali (as in milk-alkali syndrome, often seen in patients with peptic ulcers), administration of excessive amounts of I.V. fluids with high concentrations of bicarbonate or lactate, or respiratory insufficiency—all of which cause chronic hypercapnia from high levels of plasma bicarbonate.

Complications

- Coma
- Atrioventricular arrhythmias

Signs and symptoms

Clinical features of metabolic alkalosis result from the body's attempt to correct the acid-base imbalance, primarily through hypoventilation. Other manifestations include irritability, picking at bedclothes (carphology), twitching, confusion, nausea, vomiting, and diarrhea (which aggravates alkalosis). Cardiovascular abnormalities (such as atrial tachycardia) and respiratory disturbances (such as cyanosis and apnea) also occur. In the alkalotic patient, diminished peripheral blood flow during repeated blood pressure checks may provoke carpopedal spasm in

the hand—a possible sign of impending tetany (Trousseau's sign). Uncorrected metabolic alkalosis may progress to seizures and coma.

Diagnosis

CONFIRMING DIAGNOSIS

Blood pH level greater than 7.45 and bicarbonate levels above 29 mEq/L confirm the diagnosis. A partial pressure of carbon dioxide above 45 mm Hg indicates attempts at respiratory compensation. Serum electrolyte studies show low potassium, calcium, and chloride levels.

Other characteristic findings include:

- Urine pH is usually about 7.0.
- Urinalysis reveals alkalinity after the renal compensatory mechanism begins to excrete bicarbonate.
- Electrocardiogram may show low T wave, merging with a U wave (secondary to hypocalcemia from metabolic alkalosis), and atrial or sinus tachycardia.

Treatment

Treatment aims to correct the underlying cause of metabolic alkalosis. Therapy for severe alkalosis may include cautious administration of ammonium chloride I.V. or hydrochloric acid to release hydrogen chloride and restore concentration of extracellular fluid and chloride levels. Potassium chloride and normal saline solution (except in the presence of heart failure) are usually sufficient to replace losses from gastric drainage. Electrolyte replacement with potassium chloride and discontinuing diuretics correct metabolic alkalosis resulting from potent diuretic therapy.

Oral or I.V. acetazolamide, which enhances renal bicarbonate excretion, may be prescribed to correct metabolic alkalosis without rapid volume expansion. Because acetazolamide also enhances potassium excretion, potassium may have to be administered before giving this drug.

Special considerations

Structure the care plan around cautious I.V. therapy, keen observation, and strict monitoring of the patient's status.

- Dilute potassium when giving I.V. containing potassium salts. Monitor the infusion rate to prevent damage to blood vessels; watch for signs of phlebitis. When administering ammonium chloride 0.9%, limit the infusion rate to 1 L in 4 hours; faster administration may cause hemolysis of red blood cells. Avoid overdosage because it may cause overcorrection to metabolic acidosis. Don't give ammonium chloride with signs of hepatic or renal disease; instead, use hydrochloric acid.
- Watch closely for signs of muscle weakness, tetany, or decreased activity. Monitor vital signs frequently and record intake and output to evaluate respiratory, fluid, and electrolyte status. Remember, respiratory rate usually decreases in an effort to compensate for alkalosis. Hypotension and

  tachycardia may indicate electrolyte imbalance, especially hypokalemia.
- Observe seizure precautions.

PREVENTION

To prevent metabolic alkalosis, warn patients against overusing alkaline agents. Irrigate NG tubes with isotonic saline solution instead of plain water to prevent loss of gastric electrolytes. Monitor I.V. fluid concentrations of bicarbonate or lactate. Teach patients with ulcers to recognize signs of milk-alkali syndrome: a distaste for milk, anorexia, weakness, and lethargy.

Selected references

Clark, L.T., and El-Atat, F.“Metabolic Syndrome in African Americans: Implications for Preventing Coronary Heart Disease,” *Clinical Cardiology* 30(4):161-64, April 18, 2007.