1 - Nutritional Disorders

Chapter 1. Nutrition: General Considerations

Introduction

Nutrition is the science of food and its relationship to health. Nutrients are chemicals in foods that are used by the body for growth, maintenance, and energy. Nutrients that cannot be synthesized by the body and thus must be derived from the diet are considered essential. They include vitamins, minerals, some amino acids, and some fatty acids. Nutrients that the body can synthesize from other compounds, although they may also be derived from the diet, are considered nonessential. Macronutrients are required by the body in relatively large amounts; micronutrients are needed in minute amounts.

Lack of nutrients can result in deficiency syndromes (eg, kwashiorkor, pellagra) or other disorders (see p. 9). Excess intake of macronutrients can lead to obesity (see p. 56) and related disorders; excess intake of micro-nutrients can be toxic. Also, the balance of various types of nutrients, such as how much usaturated vs saturated fat is consumed, can influence the development of disorders.

Macronutrients

Macronutrients constitute the bulk of the diet and supply energy and many essential nutrients. Carbohydrates, proteins (including essential amino acids), fats (including essential fatty acids), macrominerals, and water are macronutrients. Carbohydrates, fats, and proteins are interchangeable as sources of energy; fats yield 9 kcal/g (37.8 kJ/g); proteins and carbohydrates yield 4 kcal/g (16.8 kJ/g).

Carbohydrates: Dietary carbohydrates are broken down into glucose and other monosaccharides. Carbohydrates increase blood glucose levels, supplying energy. Simple carbohydrates are composed of small molecules, generally monosaccharides or disaccharides, which increase blood glucose levels rapidly. Complex carbohydrates are composed of larger molecules, which are broken down into monosaccharides. Complex carbohydrates increase blood glucose levels more slowly but for a longer time. Glucose and sucrose are simple carbohydrates; starches and fiber are complex carbohydrates.

The glycemic index measures how rapidly consumption of a carbohydrate increases plasma glucose levels. Values range from 1 (the slowest increase) to 100 (the fastest increase, equivalent to pure glucose—see Table 1-1). However, the actual rate of increase also depends on what foods are consumed with the carbohydrate.

Carbohydrates with a high glycemic index may increase plasma glucose to high levels rapidly. It is hypothesized that, as a result, insulin levels increase, inducing hypoglycemia and hunger, which tends to lead to consumption of excess calories and weight gain. Carbohydrates with a low glycemic index increase plasma glucose levels slowly, resulting in lower postprandial insulin levels and less hunger, which probably makes consumption of excess calories less likely. These effects are predicted to result in a more favorable lipid profile and a decreased risk of obesity, diabetes mellitus, and complications of diabetes if present.

Proteins: Dietary proteins are broken down into peptides and amino acids. Proteins are required for tissue maintenance, replacement, function, and growth. However, if the body is not getting enough calories from dietary sources or tissue stores (particularly of fat), protein may be used for energy.

As the body uses dietary protein for tissue production, there is a net gain of protein (positive nitrogen balance). During catabolic

[**Table 1-1.** Glycemic Index of Some Foods]

states (eg, starvation, infections, burns), more protein may be used (because body tissues are broken down) than is absorbed, resulting in a net loss of protein (negative nitrogen balance). Nitrogen balance is best determined by subtracting the amount of nitrogen excreted in urine and feces from the amount of

nitrogen consumed.

Of the 20 amino acids, 9 are essential amino acids (EAAs); they cannot be synthesized and must be obtained from the diet. All people require 8 EAAs; infants also require histidine.

The weight-adjusted requirement for dietary protein correlates with growth rate, which decreases from infancy until adulthood. The daily dietary protein requirement decreases from 2.2 g/kg in 3-mo-old infants to 1.2 g/kg in 5-yr-old children and to 0.8 g/kg in adults. Protein requirements correspond to EAA requirements (see Table 1-2). Adults trying to increase muscle mass need very little extra protein beyond the requirements in the table.

The amino acid composition of protein varies widely. Biological value (BV) reflects the similarity in amino acid composition of protein to that of animal tissues; thus, BV indicates what percentage of a dietary protein provides EAAs for the body. A perfect match is egg protein, with a value of 100. Animal proteins in milk and meat have a high BV (~90); proteins in cereal and vegetables have a lower BV (~40), and some derived proteins (eg, gelatin) have a BV of 0. The extent to which dietary proteins supply each other's missing amino acids (complementarity) determines the overall BV of the diet. The recommended daily allowances (RDA) for protein assumes that the average mixed diet has a BV of 70.

Fats: Fats are broken down into fatty acids and glycerol. Fats are required for tissue growth and hormone production. Saturated fatty acids, common in animal fats, tend to be solid at room temperature. Except for palm and coconut oils, fats derived from plants tend to be liquid at room temperature; these fats contain high levels of monounsaturated fatty acids or polyunsaturated fatty acids (PUFAs).

Partial hydrogenation of unsaturated fatty acids (as occurs during food manufacturing) produces trans fatty acids, which are solid or semisolid at room temperature. In the US, the main dietary source of trans fatty acids is partially hydrogenated vegetable oils, used in manufacturing certain foods (eg, cookies, crackers, chips) to prolong shelf-life. Trans fatty acids may elevate LDL cholesterol and lower HDL; they may also independently increase the risk of coronary artery disease.

Essential fatty acids (EFAs) are linoleic acid, an ω-6 (n-6) fatty acid, and linolenic acid, an ω-3 (n-3) fatty acid. Other ω-6 acids (eg, arachidonic acid) and other ω-3 fatty acids (eg, eicosapentaenoic acid, docosahexaenoic acid) are required by the body but can be synthesized from EFAs.

EFAs (see also p. 19) are needed for the formation of various eicosanoids (biologically active lipids), including prostaglandins, thromboxanes, prostacyclins, and leukotrienes. Consumption of ω-3 fatty acids may decrease the risk of coronary artery disease.

[**Table 1-2.** Essential Amino Acid Requirements in mg/kg Body Weight]

Requirements for EFAs vary by age. Adults require amounts of linoleic acid equal to at least 2% of total caloric needs and linolenic acid equal to at least 0.5%. Vegetable oils provide linoleic acid and linolenic acid. Oils made from safflower, sunflower, corn, soya, primrose, pumpkin, and wheat germ provide large amounts of linoleic acid. Marine fish oils and oils made from flax-seeds, pumpkin, soy, and canola provide large amounts of linolenic acid. Marine fish oils also provide some other ω-3 fatty acids in large amounts.

Macrominerals: Na, Cl, K, Ca, P, and Mg are required in relatively large amounts per day (see Tables 1-3, 1-4, and 5-2).

Water: Water is considered a macronutrient because it is required in amounts of 1 mL/kcal (0.24 mL/kJ) of energy expended, or about 2500 mL/day. Needs vary with fever, physical activity, and changes in climate and humidity.

[**Table 1-3.** Macrominerals]

[**Table 1-4.** Recommended Dietary Reference Intakes* for Some Macronutrients, Food and Nutrition Board, Institute of Medicine of the National Academies]

Micronutrients

Vitamins and minerals required in minute amounts (trace minerals) are micronutrients (see Chs. 4 and 5).

Water-soluble vitamins are vitamin C (ascorbic acid) and 8 members of the vitamin B complex: biotin, folate, niacin, pantothenic acid, riboflavin (vitamin B_2), thiamin (vitamin B_1), vitamin B_6 (pyridoxine), and vitamin B_{12} (cobalamin).

Fat-soluble vitamins are vitamins A (retinol), D (cholecalciferol and ergocalciferol), E (α-tocopherol), and K (phylloquinone and menaquinone).

Only vitamins A, E, and B_{12} are stored to any significant extent in the body; the other vitamins must be consumed regularly to maintain tissue health.

Essential trace minerals include chromium, copper, iodine, iron, manganese, molybdenum, selenium, and zinc. Except for chromium, each of these is incorporated into enzymes or hormones required in metabolism. Except for deficiencies of iron and zinc, micromineral deficiencies are uncommon in developed countries (see Ch. 5).

Other minerals (eg, aluminum, arsenic, boron, cobalt, fluoride, nickel, silicon, vanadium) have not been proved essential for people. Fluoride, although not essential, helps prevent tooth decay by forming a compound with Ca (CaF_2), which stabilizes the mineral matrix in teeth.

All trace minerals are toxic at high levels, and some (arsenic, nickel, and chromium) may cause cancer.

Other Dietary Substances

The daily human diet typically contains as many as 100,000 chemicals (eg, coffee contains 1000). Of these, only 300 are nutrients, only some of which are essential. However, many nonnutrients in foods are useful. For example, food additives (eg, preservatives, emulsifiers, antioxidants, stabilizers) improve the production and stability of foods. Trace components (eg, spices, flavors, odors, colors, phytochemicals, many other natural products) improve appearance and taste.

Fiber: Fiber occurs in various forms (eg, cellulose, hemicellulose, pectin, gums). It increases GI motility, prevents constipation, and helps control diverticular disease. Fiber is thought to accelerate the elimination of cancer-causing substances produced by bacteria in the large intestine. Epidemiologic evidence suggests an association between colon cancer and low fiber intake and a beneficial effect of fiber in patients with functional bowel disorders, Crohn's disease, obesity, and hemorrhoids. Soluble fiber (present in fruits, vegetables, oats, barley, and legumes) reduces the postprandial increase in blood glucose and insulin and can reduce cholesterol levels.

The typical Western diet is low in fiber (about 12 g/day) because of a high intake of highly refined wheat flour and a low intake of fruits and vegetables. Increasing fiber intake to about 30 g/day by consuming more vegetables, fruits, and high-fiber cereals and grains is generally recommended. However, very high fiber intake may reduce absorption of certain minerals.

Nutritional Requirements

Good nutrition aims to achieve and maintain a desirable body composition and high potential for physical and mental work. Balancing energy intake with energy expenditure is necessary for a desirable body weight. Energy expenditure depends on age, sex, weight (see Table 1-4), and metabolic and physical activity. If energy intake exceeds expenditure, weight is gained. Taking in about 100 calories/day more than needed results in a weight gain of about 4 to 5 kg in a year. If energy intake is less than expenditure, weight is lost.

Daily dietary requirements for essential nutrients also depend on age, sex, weight, and metabolic and physical activity. Every 5 yr, the Food and Nutrition Board of the National Academy of Sciences/National Research Council and the US Department of Agriculture (USDA) issues the dietary reference intakes (DRIs) for protein, energy, and some vitamins and minerals (see Tables 1-4, 4-1, and 5-2). For vitamins and minerals about which less is known, safe and adequate daily dietary intakes are estimated.

Pregnant women (see p. 2608) and infants (see p. 2703) have special nutritional needs.

The USDA publishes the Food Guide Pyramid, which specifies the number of recommended daily servings of various food groups. The recommendations are individualized based on age, sex, and physical activity (see Table 1-5). Generally, the recommended intake decreases with aging because physical activity tends to decrease, resulting in less energy expended. The new Food Guide Pyramid emphasizes the following:

• Increasing consumption of whole grains

• Increasing consumption of vegetables and fruits

• Substituting fat-free or low-fat milk products (or equivalents) for whole-fat milk products

• Reducing consumption of saturated fats and trans fatty acids

• Exercising regularly

Adequate fluid intake is also important.

Fats should constitute ≤ 30% of total calories, and saturated and trans fatty acids should constitute < 10%. Excess intake of saturated fats contributes to atherosclerosis. Substituting polyunsaturated fatty acids for saturated fats can decrease the risk of atherosclerosis. Routine use of nutritional supplements is not necessary or beneficial; some supplements can be harmful. For example, excess vitamin A can lead to hypervitaminosis A, with headaches, osteoporosis, and rash.

Nutrition in Clinical Medicine

Nutritional deficiencies can often worsen health outcomes (whether a disorder is present or not), and some disorders (eg, malabsorption) can cause nutritional deficiencies. Also, many patients (eg, elderly patients during acute hospitalization) have unsuspected nutritional deficiencies that require treatment. Many medical centers have multi-disciplinary nutrition support teams of physicians, nurses, dietitians, and pharmacists to help the clinician prevent, diagnose, and treat occult nutritional deficiencies.

Overnutrition may contribute to chronic disorders, such as cancer, hypertension, obesity, diabetes mellitus, and coronary artery disease. Dietary restrictions are necessary in many hereditary metabolic disorders (eg, galactosemia, phenylketonuria).

Evaluation of Nutritional Status

Indications for nutritional evaluation include undesirable body weight or body composition, suspicion of specific deficiencies or toxicities

[**Table 1-5.** Recommended Dietary Intake for 40-yr-Olds with Moderate Physical Activity*]

of essential nutrients, and, in infants and children, insufficient growth or development. Nutritional status should be evaluated routinely as part of the clinical examination for infants and children, the elderly, people taking several drugs, people with psychiatric disorders, and people with systemic disorders that last longer than several days.

Evaluating general nutritional status includes history, physical examination, and sometimes tests. If undernutrition is suspected, laboratory tests (eg, albumin levels) and skin tests for delayed hypersensitivity may be done (see p. 13). Body composition analysis (eg, skinfold measurements, bioelectrical impedance analysis) is used to estimate percentage of body fat and to evaluate obesity (see p. 58).

History includes questions about dietary intake, weight change, and risk factors for nutritional deficiencies and a focused review of systems (see Table 2-1 on p. 11). A dietitian can obtain a more detailed dietary history. It usually includes a list of foods eaten within the previous 24 h and a food questionnaire. A food diary may be used to record all foods eaten. The weighed ad libitum diet, in which the patient weighs and writes down all foods consumed, is the most accurate record.

A complete physical examination, including measurement of height and weight and distribution of body fat, should be done. Body mass index (BMI)—weight(kg)/height(m)^2, which adjusts weight for height (see Table 6-2 on p. 59), is more accurate than height and weight tables. There are standards for growth and weight gain in infants, children, and adolescents (see p. 2756).

Distribution of body fat is important. Disproportionate truncal obesity (ie, waist/hip ratio > 0.8) is associated with cardiovascular and cerebrovascular disorders, hypertension, and diabetes mellitus more often than fat located elsewhere. Measuring waist circumference in patients with a BMI of < 35 helps determine whether they have truncal obesity and helps predict risk of diabetes, hypertension, hypercholesterolemia, and cardiovascular disorders. Risk is increased if waist circumference is > 102 cm (> 40 in) in men or > 88 cm (> 35 in) in women.

Nutrient-Drug Interactions

Nutrition can affect the body's response to drugs; conversely, drugs can affect the body's nutrition.

Foods can enhance, delay, or decrease drug absorption. Foods impair absorption of many antibiotics. They can alter metabolism of drugs; eg, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450. Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers). Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs. Some foods affect the body's response to drugs. For example, tyramine, a component of cheese and a potent vasoconstrictor, can cause hypertensive crisis in some patients who take monoamine oxidase inhibitors and eat cheese.

Nutritional deficiencies can affect drug absorption and metabolism. Severe energy and protein deficiencies reduce enzyme tissue concentrations and may impair the response to drugs by reducing absorption or protein binding and causing liver dysfunction. Changes in the GI tract can impair absorption and affect the response to a drug. Deficiency of Ca, Mg, or zinc may impair drug metabolism. Vitamin C deficiency decreases activity of drug-metabolizing enzymes, especially in the elderly.

Many drugs affect appetite, food absorption, and tissue metabolism (see Table 1-6). Some drugs (eg, metoclopramide) increase GI motility, decreasing food absorption. Other drugs (eg, opioids, anticholinergics) decrease GI motility. Some drugs are better tolerated if taken with food.

Certain drugs affect mineral metabolism. For example, diuretics, especially thiazides, and corticosteroids can deplete body K, increasing susceptibility to digoxin-induced cardiac arrhythmias. Repeated use of laxatives may deplete K. Cortisol, desoxycorticosterone, and aldosterone cause marked Na and water retention, at least temporarily; retention is much less with prednisone, prednisolone, and some other corticosteroid analogs. Sulfonylureas and lithium can impair the uptake or release of iodine by the thyroid. Oral contraceptives can lower blood zinc levels and increase copper levels. Certain antibiotics (eg, tetracyclines) reduce iron absorption, as can certain foods (eg, vegetables, tea, bran).

Certain drugs affect vitamin absorption or metabolism. Ethanol impairs thiamin utilization, and isoniazid interferes with niacin and pyridoxine metabolism. Ethanol and oral contraceptives inhibit folate (folic acid)

absorption. Most patients receiving phenytoin, phenobarbital, primidone, or phenothiazines develop folate deficiency, probably because hepatic microsomal drug-metabolizing enzymes are affected. Folate supplements may

[**Table 1-6.** Effects of Some Drugs on Nutrition]

make phenytoin less effective. Anticonvulsants can cause vitamin D deficiency. Malabsorption of vitamin B_{12} can occur with use of aminosalicylic acid, slow-release K iodide, colchicine, trifluoperazine, ethanol, and oral contraceptives. Oral contraceptives with a high progestin dose can cause depression, probably because of metabolically induced tryptophan deficiency.

Food Additives and Contaminants

Additives: Chemicals are often combined with foods to facilitate their processing and preservation or to enhance their desirability. Only amounts of additives shown to be safe by laboratory tests are permitted in commercially prepared foods.

Weighing the benefits of additives (eg, reduced waste, increased variety of available foods, protection against food-borne illness) against the risks is often complex. For example, nitrite, which is used in cured meats, inhibits the growth of *Clostridium botulinum* and improves flavor. However, nitrite converts to nitrosamines, which are carcinogens in animals. On the other hand, the amount of nitrite added to cured meat is small compared with the amount from naturally occurring food nitrates converted to nitrite by the salivary glands. Dietary vitamin C can reduce nitrite formation in the GI tract. Rarely, some additives (eg, sulfites) cause food hypersensitivity (allergy) reactions. Most of these reactions are caused by ordinary foods (see p. 1118).

Contaminants: Sometimes limited amounts of contaminants are allowed in foods because the contaminants cannot be completely eliminated without damaging the foods. Common contaminants are pesticides, heavy metals (lead, cadmium, mercury), nitrates (in green leafy vegetables), aflatoxins (in nuts and milk), growth-promoting hormones (in dairy products and meat), animal hairs and feces, and insect parts.

FDA-estimated safe levels are levels that have not caused illness or adverse effects in people. However, demonstrating a causal relationship between extremely low level exposures and adverse effects is difficult; long-term adverse effects, although unlikely, are still possible. Safe levels are often determined by consensus rather than by hard evidence.

Chapter 2. Undernutrition

Introduction

Undernutrition is a form of malnutrition. (Malnutrition also includes overnutrition—see Ch. 6). Undernutrition can result from inadequate ingestion of nutrients, malabsorption, impaired metabolism, loss of nutrients due to diarrhea, or increased nutritional requirements (as occurs in cancer or infection). Undernutrition progresses in stages; each stage usually takes considerable time to develop. First, nutrient levels in blood and tissues change, followed by intracellular changes in biochemical functions and structure. Ultimately, symptoms and signs appear.

Risk Factors

Undernutrition is associated with many disorders and circumstances, including poverty and social deprivation. Risk is also greater at certain times (ie, during infancy, early childhood, adolescence, pregnancy, breastfeeding, and old age).

Infancy and childhood: Infants and children are particularly susceptible to undernutrition because of their high demand for energy and essential nutrients. Because vitamin K does not readily cross the placenta, neonates may be deficient, so all are given a single injection of vitamin K within 1 h of birth to prevent hemorrhagic disease of the newborn, a life-threatening disorder (see pp. 46 and 2783). Infants fed only breast milk, which is typically low in vitamin D, are given supplemental vitamin D; they can develop vitamin B_{12} deficiency if the mother is a vegan. Inadequately fed infants and children are at risk of protein-energy undernutrition (PEU—previously called protein-energy malnutrition) and deficiencies of iron, folate (folic acid), vitamins A and C, copper, and zinc. During adolescence, nutritional requirements increase because the growth rate accelerates. Anorexia nervosa (see p. 1535) may affect adolescent girls in particular.

Pregnancy and breastfeeding: Requirements for nutrients increase during pregnancy and breastfeeding. Aberrations of diet, including pica (consumption of nonnutritive substances, such as clay and charcoal), may occur during pregnancy. Anemia due to iron deficiency is common, as is anemia due to folate deficiency, especially among women who have taken oral contraceptives. Vitamin D deficiency is common during late pregnancy, predisposing the child to decreased bone mass.

Old age: Aging—even when disease or dietary deficiency is absent—leads to sarcopenia (progressive loss of lean body mass), starting after age 40 and eventually amounting to a muscle loss of about 10 kg (22 lb) in men and 5 kg (11 lb) in women. Undernutrition contributes to sarcopenia, and sarcopenia accounts for many of the complications of undernutrition (eg, decreased nitrogen balance, increased susceptibility to infections). Causes of sarcopenia include the following:

- Decreased physical activity
- Decreased food intake
- Increased levels of cytokines (particularly interleukin-6)
- Decreased levels of growth hormone and mechano growth factor (insulin-like growth factor-3)
- In men, decreasing androgen levels

Aging decreases basal metabolic rate (due mainly to decreased fat-free mass), total body weight, height, and skeletal mass; aging increases mean body fat (as a percentage of body weight) to about 30% (from 20%) in men and to 40% (from 27%) in women.

From age 20 to 80, food intake decreases, especially in men. Anorexia due to aging itself has many causes, including reduced adaptive relaxation of the stomach's fundus, increased release and activity of

cholecystokinin (which produces satiation), and increased leptin (an anorectic hormone produced by fat cells). Diminished taste and smell can decrease eating pleasure but usually decrease food intake only slightly. Anorexia may have other causes (eg, loneliness, inability to shop or prepare meals, dementia, some chronic disorders, use of certain drugs). Depression is a common cause. Occasionally, anorexia nervosa (sometimes called anorexia tardive in the elderly), paranoia, or mania interferes with eating. Dental problems limit the ability to chew and subsequently to digest foods. Swallowing difficulties (eg, due to strokes, other neurologic disorders, esophageal candidiasis, or xerostomia) are common. Poverty or functional impairment limits access to nutrients.

The institutionalized elderly are at particular risk of PEU. They are often confused and may be unable to express hunger or preferences for foods. They may be physically unable to feed themselves. Chewing or swallowing may be very slow, making it tedious for another person to feed them enough food.

In the elderly, particularly the institutionalized elderly, inadequate intake and often decreased absorption or synthesis of vitamin D, increased demand for vitamin D, and inadequate exposure to sunshine contribute to osteomalacia (see p. 41).

Disorders and medical procedures: Diabetes, some chronic disorders that affect the GI tract, intestinal resection, and certain other GI surgical procedures tend to impair absorption of fat-soluble vitamins, vitamin B_{12}, Ca, and iron. Gluten enteropathy, pancreatic insufficiency, or other disorders can result in malabsorption. Decreased absorption possibly contributes to iron deficiency and osteoporosis. Liver disorders impair storage of vitamins A and B_{12} and interfere with metabolism of protein and energy sources. Renal insufficiency predisposes to protein, iron, and vitamin D deficiencies. Anorexia causes some patients with cancer or depression and many with AIDS to consume inadequate amounts of food. Infections, trauma, hyperthyroidism, extensive burns, and prolonged fever increase metabolic demands. Any condition that increases cytokines may be accompanied by muscle loss, lipolysis, low albumin levels, and anorexia.

Vegetarian diets: Iron deficiency can occur in ovo-lacto vegetarians (although such a diet can be compatible with good health). Vegans may develop vitamin B_{12} deficiency unless they consume yeast extracts or Asian-style fermented foods. Their intake of Ca, iron, and zinc also tends to be low. A fruit-only diet is not recommended because it is deficient in protein, Na, and many micronutrients.

Fad diets: Some fad diets result in vitamin, mineral, and protein deficiencies; cardiac, renal, and metabolic disorders; and sometimes death. Very low calorie diets (< 400 kcal/day) cannot sustain health for long.

Drugs and nutritional supplements: Many drugs (eg, appetite suppressants, digoxin) decrease appetite; others impair nutrient absorption or metabolism. Some drugs (eg, stimulants) have catabolic effects. Certain drugs can impair absorption of many nutrients; eg, anticonvulsants can impair absorption of vitamins.

Alcohol or drug dependency: Patients with alcohol or drug dependency may neglect their nutritional needs. Absorption and metabolism of nutrients may also be impaired. IV drug addicts typically become undernourished, as do

[
Table 2-1. Symptoms and Signs of Nutritional Deficiency]

alcoholics who consume ≥ 1 quart of hard liquor/day. Alcoholism can cause deficiencies of Mg, zinc, and certain vitamins, including thiamin.

Symptoms and Signs

Symptoms vary depending on the cause and type of undernutrition (see p. 15 and Chs. 4 and 5).

Evaluation

Diagnosis is based on results of medical and diet histories, physical examination, body composition analysis (see p. 58), and selected laboratory tests.

History: History should include questions about dietary intake (see Fig. 2-1), recent changes in weight, and risk factors for undernutrition, including drug and alcohol use. Unintentional loss of ≥ 10% of usual body weight during a 3-mo period indicates a high probability of undernutrition. Social history should include questions about whether money is available for food and whether the patient can shop and cook.

Review of systems should focus on symptoms of nutritional deficiencies (see Table 2-1). For example, impaired night vision may indicate vitamin A deficiency.

Physical examination: Physical examination should include measurement of height and weight, inspection of body fat distribution, and anthropometric measurements of lean body mass. Body mass index (BMI = weight(kg)/height(m)^2) adjusts weight for height (see Table 6-2 on p. 59). If weight is < 80% of what is predicted for the patient's height or if BMI is ≤ 18, undernutrition should be suspected. Although these findings are useful in diagnosing undernutrition and are acceptably sensitive, they lack specificity.

[**Fig. 2-1.** Mini nutritional assessment.]

The mid upper arm muscle area estimates lean body mass. This area is derived from the triceps skinfold thickness (TSF) and mid upper arm circumference. Both are measured at the same site, with the patient's right arm in a relaxed position. The average mid upper arm circumference is about 32 ± 5 cm for men and 28 ± 6 cm for women. The formula for calculating the mid upper arm muscle area in cm^2 is as follows:

$$\frac{[\text{midarm circumference (cm)} - (3.14 \times \text{TSF cm})]^2}{4\pi} - 10\,(\text{males}) \text{ or } -6.5\,(\text{females})$$

This formula corrects the upper arm area for fat and bone. Average values for the mid upper arm muscle area are 54 ± 11 cm^2 for men and 30 ± 7 cm^2 for women. A value < 75% of this standard (depending on age) indicates depletion of lean body mass (see Table 2-2). This measurement may be affected by physical activity, genetic factors, and age-related muscle loss.

Physical examination should focus on signs of specific nutritional deficiencies. Signs of PEU (eg, edema, muscle wasting, skin changes) should be sought. Examination should also focus on signs of conditions that could predispose to nutritional deficiencies, such as dental problems. Mental status should be assessed, because depression and cognitive impairment can lead to weight loss.

The widely used Subjective Global Assessment (SGA) uses information from the patient history (eg, weight loss, change in intake, GI symptoms), physical examination findings (eg, loss of muscle and subcutaneous fat, edema, ascites), and the clinician's judgment of the patient's nutritional status. The Mini Nutritional Assessment (MNA) has been validated and is widely used, especially for elderly patients (see Fig. 2-1). The Simplified Nutrition Assessment Questionnaire (SNAQ), a simple, validated method of predicting future weight loss, may be used (see Fig. 2-2).

Testing: The extent of laboratory testing needed is unclear and may depend on the patient's circumstances. If the cause is obvious and correctable (eg, a wilderness survival situation), testing is probably of little benefit. Other patients may require more detailed evaluation.

Serum albumin measurement is the laboratory test most often used. Decreases in albumin and other proteins (eg, prealbumin [transthyretin], transferrin, retinol-binding protein) may indicate protein deficiency or PEU. As undernutrition progresses, albumin decreases slowly; prealbumin, transferrin, and retinol-binding protein decrease rapidly. Albumin measurement is inexpensive and predicts morbidity and

mortality better than measurement of the other proteins. However, the correlation of albumin with morbidity and mortality may be related to nonnutritional as well as nutritional factors. Inflammation produces cytokines that cause albumin and other nutritional protein markers to extravasate, decreasing serum levels. Because prealbumin, transferrin, and retinol-binding protein decrease more rapidly during starvation than does albumin, their measurements are sometimes used to diagnose or assess the severity of acute starvation. However, whether they are more sensitive or specific than albumin is unclear.

Total lymphocyte count, which often decreases as undernutrition progresses, may be determined. Undernutrition causes a marked decline in CD4+ T lymphocytes, so this count may not be useful in patients who have AIDS.

Skin tests using antigens can detect impaired cell-mediated immunity in PEU and in some other disorders of undernutrition (see p. 1098).

Other laboratory tests, such as measuring vitamin and mineral levels, are used selectively to diagnose specific deficiencies.

[**Table 2-2.** Mid Upper Arm Muscle Area in Adults]

[**Figure 2-2.** Simplified Nutrition Assessment Questionnaire (SNAQ).]

Protein-Energy Undernutrition

Protein-energy undernutrition (PEU), previously called protein-energy malnutrition, is an energy deficit due to chronic deficiency of all macronutrients. It commonly includes deficiencies of many micronutrients. PEU can be sudden and total (starvation) or gradual. Severity ranges from subclinical deficiencies to obvious wasting (with edema, hair loss, and skin atrophy) to starvation. Multiple organ systems are often impaired. Diagnosis usually involves laboratory testing, including serum albumin. Treatment consists of correcting fluid and electrolyte deficits with IV solutions, then gradually replenishing nutrients, orally if possible.

In developed countries, PEU is common among the institutionalized elderly (although often not suspected) and among patients with disorders that decrease appetite or impair nutrient digestion, absorption, or metabolism. In developing countries, PEU affects children who do not consume enough calories or protein.

Classification and Etiology

PEU is graded as mild, moderate, or severe. Grade is determined by calculating weight as a percentage of expected weight for length or height using international standards (normal, 90 to 110%; mild PEU, 85 to 90%; moderate, 75 to 85%; severe, <75%).

PEU may be primary or secondary. Primary PEU is caused by inadequate nutrient intake. Secondary PEU results from disorders or drugs that interfere with nutrient use.

Primary PEU: Worldwide, primary PEU occurs mostly in children and the elderly who lack access to nutrients, although a common cause in the elderly is depression. PEU can also result from fasting or anorexia nervosa. Child or elder abuse may be a cause.

In children, chronic primary PEU has 2 common forms: marasmus and kwashiorkor. The form depends on the balance of nonprotein and protein sources of energy. Starvation is an acute severe form of primary PEU.

Marasmus (also called the dry form of PEU) causes weight loss and depletion of fat and muscle. In developing countries, marasmus is the most common form of PEU in children.

Kwashiorkor (also called the wet, swollen, or edematous form) is associated with premature abandonment

of breastfeeding, which typically occurs when a younger sibling is born, displacing the older child from the breast. So children with kwashiorkor tend to be older than those with marasmus. Kwashiorkor may also result from an acute illness, often gastroenteritis or another infection (probably secondary to cytokine release), in a child who already has PEU. A diet that is more deficient in protein than energy may be more likely to cause kwashiorkor than marasmus. Less common than marasmus, kwashiorkor tends to be confined to specific parts of the world, such as rural Africa, the Caribbean, and the Pacific islands. In these areas, staple foods (eg, yams, cassavas, sweet potatoes, green bananas) are low in protein and high in carbohydrates. In kwashiorkor, cell membranes leak, causing extravasation of intravascular fluid and protein, resulting in peripheral edema.

Starvation is a complete lack of nutrients. It occasionally occurs when food is available (as in fasting or anorexia nervosa) but usually occurs because food is unavailable (eg, during famine or wilderness exposure).

Secondary PEU: This type most commonly results from the following:

- Disorders that affect GI function: These disorders can interfere with digestion (eg, pancreatic insufficiency), absorption (eg, enteritis, enteropathy), or lymphatic transport of nutrients (eg, retroperitoneal fibrosis, Milroy's disease).

- Wasting disorders: In wasting disorders (eg, AIDS, cancer) and renal failure, catabolism causes cytokine excess, resulting in undernutrition via anorexia and cachexia (wasting of muscle and fat). End-stage heart failure can cause cardiac cachexia, a severe form of undernutrition; mortality rate is particularly high. Factors contributing to cardiac cachexia may include passive hepatic congestion (causing anorexia), edema of the intestinal tract (impairing absorption), and, in advanced disease, increased O_2 requirement due to anaerobic metabolism. Wasting disorders can decrease appetite or impair metabolism of nutrients.

- Conditions that increase metabolic demands: These conditions include infections, hyperthyroidism, pheochromocytoma, other endocrine disorders, burns, trauma, surgery, and other critical illnesses.

Pathophysiology

The initial metabolic response is decreased metabolic rate. To supply energy, the body first breaks down adipose tissue. However, later when these tissues are depleted, the body may use protein for energy, resulting in a negative nitrogen balance. Visceral organs and muscle are broken down and decrease in weight. Loss of organ weight is greatest in the liver and intestine, intermediate in the heart and kidneys, and least in the nervous system.

Symptoms and Signs

Symptoms of moderate PEU can be constitutional or involve specific organ systems. Apathy and irritability are common. The patient is weak, and work capacity decreases. Cognition and sometimes consciousness are impaired. Temporary lactose deficiency and achlorhydria develop. Diarrhea is common and can be aggravated by deficiency of intestinal disaccharidases, especially lactase (see p. 157). Gonadal tissues atrophy. PEU can cause amenorrhea in women and loss of libido in men and women.

Wasting of fat and muscle is common in all forms of PEU. In adult volunteers who fasted for 30 to 40 days, weight loss was marked (25% of initial weight). If starvation is more prolonged, weight loss may reach 50% in adults and possibly more in children.

In adults, cachexia is most obvious in areas where prominent fat depots normally exist. Muscles shrink and bones protrude. The skin becomes thin, dry, inelastic, pale, and cold. The hair is dry and falls out easily, becoming sparse. Wound healing is impaired. In elderly patients, risk of hip fractures and pressure (decubitus) ulcers increases.

With acute or chronic severe PEU, heart size and cardiac output decrease; pulse slows

[
Table 2-3. Values Commonly Used to Grade the Severity of Protein-Energy Undernutrition]

and BP falls. Respiratory rate and vital capacity decrease. Body temperature falls, sometimes contributing to death. Edema, anemia, jaundice, and petechiae can develop. Liver, kidney, or heart failure may occur.

Cell-mediated immunity is impaired, increasing susceptibility to infections. Bacterial infections (eg, pneumonia, gastroenteritis, otitis media, UTIs, sepsis) are common in both forms of PEU. Infections result in release of cytokines, which cause anorexia, worsen muscle wasting, and cause a marked decrease in serum albumin levels.

Marasmus in infants causes hunger, weight loss, growth retardation, and wasting of subcutaneous fat and muscle. Ribs and facial bones appear prominent. Loose, thin skin hangs in folds.

Kwashiorkor is characterized by peripheral and periorbital edema. The abdomen protrudes because abdominal muscles are weakened, the intestine is distended, the liver enlarges, and ascites is present. The skin is dry, thin, and wrinkled; it can become hyperpigmented and fissured and later hypopigmented, friable, and atrophic. Skin in different areas of the body may be affected at different times. The hair can become thin, reddish brown, or gray. Scalp hair falls out easily, eventually becoming sparse, but eyelash hair may grow excessively. Alternating episodes of undernutrition and adequate nutrition may cause the hair to have a dramatic "striped flag" appearance. Affected children may be apathetic but become irritable when held.

Total starvation is fatal in 8 to 12 wk. Thus, certain symptoms of PEU do not have time to develop.

Diagnosis

• Diagnosis usually based on history

• To determine severity: BMI, serum albumin, total lymphocyte count, CD4+ count, serum transferrin

• To diagnose complications and consequences: CBC, electrolytes, BUN, glucose, Ca, Mg, phosphate

Diagnosis can be based on history when dietary intake is markedly inadequate. The cause of inadequate intake, particularly in children, needs to be identified. In children and adolescents, child abuse and anorexia nervosa should be considered.

Physical examination findings can usually confirm the diagnosis. Laboratory tests are required if dietary history does not clearly indicate inadequate caloric intake. Measurement of serum albumin, total lymphocyte count, CD4+ T lymphocytes, transferrin, and response to skin antigens may help determine the severity of PEU (see Table 2-3) or confirm the diagnosis in borderline cases. Many other test results may be abnormal: eg, decreased levels of hormones, vitamins, lipids, cholesterol, prealbumin, insulin growth factor-1, fibronectin, and retinol-binding protein. Urinary creatine and methylhistidine levels can be used to gauge the degree of muscle wasting. Because protein catabolism slows, urinary urea level also decreases. These findings rarely affect treatment.

Laboratory tests are required to identify causes of suspected secondary PEU. C-reactive protein or soluble interleukin-2 receptor should be measured when the cause of undernutrition is unclear; these measurements can help determine whether there is cytokine excess. Thyroid function tests may also be done.

Other laboratory tests can detect associated abnormalities that may require treatment. Serum electrolytes, BUN, glucose, and possibly levels of Ca, Mg, and phosphate should be measured. Levels of serum glucose, electrolytes (especially K, occasionally Na), phosphate, Ca, and Mg are usually low. BUN is often low unless renal failure is present. Metabolic acidosis may be present. CBC is usually obtained; normocytic anemia (usually due to protein deficiency) or microcytic anemia (due to simultaneous iron deficiency) is usually present.

Stool cultures should be obtained and checked for ova and parasites if diarrhea is severe or does not resolve with treatment. Sometimes urinalysis, urine culture, blood cultures, tuberculin testing, and a chest x-ray are used to diagnose occult infections because people with PEU may have a muted response to infections.

Prognosis

Children: In children, mortality varies from 5 to 40%. Mortality rates are lower in children with mild PEU and those given intensive care. Death in the first days of treatment is usually due to electrolyte deficits, sepsis, hypothermia, or heart failure. Impaired consciousness, jaundice, petechiae, hyponatremia, and persistent diarrhea are ominous signs. Resolution of apathy, edema, and anorexia is a favorable sign. Recovery is more rapid in kwashiorkor than in marasmus.

Long-term effects of PEU in children are not fully documented. Some children develop chronic malabsorption and pancreatic insufficiency. In very young children, mild intellectual disability may develop and persist until at least school age. Permanent cognitive impairment may occur, depending on the duration, severity, and age at onset of PEU.

Adults: In adults, PEU can result in morbidity and mortality (eg, progressive weight loss increases mortality rate for elderly patients in nursing homes). In elderly patients, PEU increases the risk of morbidity and mortality due to surgery, infections, or other disorders. Except when organ failure occurs, treatment is uniformly successful.

Treatment

• Usually, oral feeding

• Possibly avoidance of lactose (eg, if persistent diarrhea suggests lactose intolerance)

• Supportive care (eg, environmental changes, assistance with feeding, orexigenic drugs)

• For children, feeding delayed 24 to 48 h

Worldwide, the most important preventive strategy is to reduce poverty and improve nutritional education and public health measures.

Mild or moderate PEU, including brief starvation, can be treated by providing a balanced diet, preferably orally. Liquid oral food supplements (usually lactose-free) can be used when solid food cannot be adequately ingested. Diarrhea often complicates oral feeding because starvation makes the GI tract more likely to move bacteria into Peyer's patches, facilitating infectious diarrhea. If diarrhea persists (suggesting lactose intolerance), yogurt-based rather than milk-based formulas are given because people with lactose intolerance can tolerate yogurt. Patients should also be given a multivitamin supplement.

Severe PEU or prolonged starvation requires treatment in a hospital with a controlled diet. The first priority is to correct fluid and electrolyte abnormalities (see Ch. 97) and treat infections. Next is to supply macronutrients orally or, if necessary (eg, when swallowing is difficult), through a feeding tube, a nasogastric tube (usually), or a gastrostomy tube. Parenteral nutrition is indicated if malabsorption is severe (see p. 23).

Other treatments may be needed to correct specific deficiencies, which may become evident as weight increases. To avoid deficiencies, patients should take micronutrients at about twice the recommended daily allowance (RDA) until recovery is complete.

Children: Underlying disorders should be treated. For children with diarrhea, feeding may be delayed 24 to 48 h to avoid making the diarrhea worse; during this interval, children require oral or IV rehydration. Feedings are given often (6 to 12 times/day) but, to avoid overwhelming the limited intestinal absorptive capacity, are limited to small amounts (< 100 mL). During the first week, milk-based formulas with supplements added are usually given in progressively increasing amounts; after a week, the full amounts

of 175 kcal/kg and 4 g of protein/kg can be given. Twice the RDA of micronutrients should be given, using commercial multivitamin supplements. After 4 wk, the formula can be replaced with whole milk plus cod liver oil and solid foods, including eggs, fruit, meats, and yeast.

Energy distribution among macronutrients should be about 16% protein, 50% fat, and 34% carbohydrate. An example is a combination of powdered cow's skimmed milk (110 g), sucrose (100 g), vegetable oil (70 g), and water (900 mL). Many other formulas (eg, whole [full-fat] fresh milk plus corn oil and maltodextrin) can be used. Milk powders used in formulas are diluted with water.

Usually, supplements should be added to formulas:

- Mg 0.4 mEq/kg/day IM is given for 7 days.
- B-complex vitamins at twice the RDA are given parenterally for the first 3 days, usually with vitamin A, phosphorus, zinc, manganese, copper, iodine, fluoride, molybdenum, and selenium.
- Because absorption of oral iron is poor in children with PEU, oral or IM iron supplementation may be necessary.

Parents are taught about nutritional requirements.

Adults: Underlying disorders should be treated. For example, if AIDS or cancer results in excess cytokine production, megestrol acetate or medroxyprogesterone may improve food intake. However, because these drugs dramatically decrease testosterone in men (possibly causing muscle loss), testosterone should be replaced. Because these drugs can cause adrenal insufficiency, they should be used only short-term (< 3 mo).

In patients with functional limitations, home delivery of meals and feeding assistance are key.

An orexigenic drug, such as the cannabis extract dronabinol, should be given to patients with anorexia when no cause is obvious or to patients at the end of life when anorexia impairs quality of life. An anabolic steroid (eg, enanthate, nandrolone, testosterone) or growth hormone can benefit patients with cachexia due to renal failure and possibly elderly patients (eg, by increasing lean body mass or possibly by improving function).

Correction of PEU in adults generally resembles that in children; feedings are often limited to small amounts. However, for most adults, feeding does not need to be delayed. A commercial formula for oral feeding can be used. Daily nutrient supply should be given at a rate of 60 kcal/kg and 1.2 to 2 g of protein/kg. If liquid oral supplements are used with solid food, they should be given at least 1 h before meals so that the amount of food eaten at the meal is not reduced.

Treatment of institutionalized elderly patients with PEU requires multiple interventions:

- Environmental measures (eg, making the dining area more attractive)
- Feeding assistance
- Changes in diet (eg, use of food enhancers and caloric supplements between meals)
- Treatment of depression and other underlying disorders
- Use of orexigenics, anabolic steroids, or both

The long-term use of gastrostomy tube feeding is essential for patients with severe dysphagia; its use in patients with dementia is controversial. Increasing evidence supports the avoidance of unpalatable therapeutic diets (eg, low salt, diabetic, low cholesterol) in institutionalized patients because these diets decrease food intake and may cause severe PEU.

Complications of treatment: Treatment of PEU can cause complications (refeeding syndrome), including fluid overload, electrolyte deficits, hyperglycemia, cardiac arrhythmias, and diarrhea. Diarrhea is usually mild and resolves; however, diarrhea in patients with severe PEU occasionally causes severe dehydration or death. Causes of diarrhea (eg, sorbitol used in elixir tube feedings, *Clostridium difficile* if the patient has received an antibiotic) may be correctable. Osmotic diarrhea due to excess calories is rare in adults and should be considered only when other causes have been excluded.

Because PEU can impair cardiac and renal function, hydration can cause intravascular volume overload. Treatment decreases extra-cellular K and Mg. Depletion of K or Mg may cause arrhythmias. Carbohydrate metabolism that occurs during treatment stimulates insulin release, which drives phosphate into cells. Hypophosphatemia can cause muscle weakness, paresthesias, seizures, coma, and arrhythmias. Because phosphate levels can change rapidly during parenteral feeding, levels should be measured regularly.

During treatment, endogenous insulin may become ineffective, leading to hyperglycemia. Dehydration and hyperosmolarity can result. Fatal ventricular arrhythmias can develop, possibly caused by a prolonged QT interval.

Carnitine Deficiency

Carnitine deficiency results from inadequate intake of or inability to metabolize the amino acid carnitine. It can cause a heterogeneous group of disorders. Muscle metabolism is impaired, causing myopathy, hypoglycemia, or cardiomyopathy. Infants typically present with hypoglycemic, hypoketotic encephalopathy. Most often, treatment consists of dietary L-carnitine.

The amino acid carnitine is required for the transport of long-chain fatty acyl coenzyme A (CoA) esters into myocyte mitochondria, where they are oxidized for energy. Carnitine is obtained from foods, particularly animal-based foods, and via endogenous synthesis.

Causes of carnitine deficiency include the following:

- Inadequate intake (eg, due to fad diets, lack of access, or long-term TPN)
- Inability to metabolize carnitine due to enzyme deficiencies (eg, carnitine palmitoyltransferase deficiency, methylmalonicaciduria, propionicacidemia, isovalericacidemia)
- Decreased endogenous synthesis of carnitine due to a severe liver disorder
- Excess loss of carnitine due to diarrhea, diuresis, or hemodialysis
- A hereditary disorder in which carnitine leaks from renal tubules
- Increased requirements for carnitine when ketosis is present or demand for fat oxidation is high (eg, during a critical illness such as sepsis or major burns; after major surgery of the GI tract)
- Decreased muscle carnitine levels due to mitochondrial impairment (eg, due to use of zidovudine)
- Use of valproate

The deficiency may be generalized (systemic) or may affect mainly muscle (myopathic).

Symptoms and Signs

Symptoms and the age at which symptoms appear depend on the cause. Carnitine deficiency may cause muscle necrosis, myoglobinuria, lipid-storage myopathy, hypoglycemia, fatty liver, and hyperammonemia with muscle aches, fatigue, confusion, and cardiomyopathy.

Diagnosis

In neonates, carnitine palmitoyltransferase deficiency is diagnosed using mass spectrometry to screen blood. Prenatal diagnosis may be possible using amniotic villous cells. In adults, the definitive diagnosis is based on acylcarnitine levels in serum, urine, and tissues (muscle and liver for systemic deficiency; muscle only for myopathic deficiency).

Treatment

• Avoidance of fasting and strenuous exercise

• Dietary interventions, based on cause

Carnitine deficiency due to inadequate dietary intake, increased requirements, excess losses, decreased synthesis, or (sometimes) enzyme deficiencies can be treated by giving L-carnitine 25 mg/kg po q 6 h.

All patients must avoid fasting and strenuous exercise. Consuming uncooked cornstarch at bedtime prevents early morning hypoglycemia. Some patients require supplementation with medium-chain triglycerides and essential fatty acids (eg, linoleic acid, linolenic acid). Patients with a fatty acid oxidation disorder require a high-carbohydrate, low-fat diet.

Essential Fatty Acid Deficiency

Essential fatty acid (EFA) deficiency is rare, occurring most often in infants fed diets deficient in EFAs. Signs include scaly dermatitis, alopecia, thrombocytopenia, and, in children, growth retardation. Diagnosis is clinical. Dietary replenishment of EFAs reverses the deficiency.

The EFAs linoleic and linolenic acid are substrates for the endogenous synthesis of other fatty acids that are needed for many physiologic processes, including maintaining the integrity of skin and cell membranes and synthesizing prostaglandins and leukotrienes. For example, eicosapentaenoic acid and docosahexaenoic acid, synthesized from EFAs, are important components of the brain and retina.

For EFA deficiency to develop, dietary intake must be very low. Even small amounts of EFAs can prevent EFA deficiency. Cow's milk has only about 25% of the linoleic acid in human milk, but when ingested in normal amounts, it has enough linoleic acid to prevent EFA deficiency. Total fat intake of people in many developing countries may be very low, but the fat is often vegetable based, with large amounts of linoleic acid and enough linolenic acid to prevent EFA deficiency.

Babies fed a formula low in linoleic acid, such as a skim-milk formula, can develop EFA deficiency. EFA deficiency used to result from long-term TPN if fat was not included. But now, most TPN solutions include fat emulsions to prevent EFA deficiency. In patients with fat malabsorption or increased metabolic needs (eg, because of surgery, multiple trauma, or burns), laboratory evidence of EFA deficiency may be present without clinical signs.

Dermatitis due to EFA deficiency is generalized and scaly; in infants, it can resemble congenital ichthyosis. The dermatitis increases water loss from the skin.

Diagnosis is usually clinical; however, laboratory assays are now available in large research centers.

Treatment consists of dietary EFAs, reversing the deficiency.

Chapter 3. Nutritional Support

Introduction

Many undernourished patients need nutritional support, which aims to increase lean body mass. Oral feeding can be difficult for some patients with anorexia or with eating or absorption problems. Behavioral measures that sometimes enhance oral intake include the following:

• Encouraging patients to eat

• Heating or seasoning foods

• Providing favorite or strongly flavored foods

• Encouraging patients to eat small portions

• Scheduling around meals

• Assisting patients with feeding

If behavioral measures are ineffective, nutritional support—oral, enteral tube, or parenteral nutrition—is indicated, except sometimes for dying or severely demented patients (see p. 25).

Predicting Nutritional Requirements

Nutritional requirements are predicted so that interventions can be planned. Requirements can be estimated by formulas or measured by indirect calorimetry. Indirect calorimetry requires use of a metabolic cart (a closed rebreathing system that determines energy expenditure based on total CO_2 production), which requires special expertise and is not always available. Thus, total energy expenditure (TEE) and protein requirements usually are estimated.

Energy expenditure: TEE varies based on the patient's weight, activity level, and degree of metabolic stress (metabolic demands); TEE ranges from 25 kcal/kg/day for people who are sedentary and not under stress to about 40 kcal/kg/day for people who are critically ill. TEE equals the sum of

• Resting metabolic rate (RMR, or resting energy expenditure rate), which is normally about 70% of TEE

• Energy dissipated by metabolism of food (10% of TEE)

• Energy expended during physical activity (20% of TEE)

Undernutrition can decrease RMR up to 20%. Conditions that increase metabolic stress (eg, critical illness, infection, inflammation, trauma, surgery) can increase RMR but rarely by > 50%.

The Mifflin-St. Jeor equation estimates RMR more precisely and with fewer errors than the commonly used Harris-Benedict equation, usually providing results that are within 20% of those measured by indirect calorimetry. The Mifflin-St. Jeor equation estimates RMR as follows:

Men: kcal / day = 66 + (13.7 × wt[kg]) + (5 × height[cm]) - (6.8 × age)
Women: kcal / day = 665 + (9.6 × wt[kg]) + (1.8 × height[cm]) - (4.7 × age)

TEE can be estimated by adding about 10% (for sedentary people) to about 40% (for people who are critically ill) to RMR.

Protein requirements: For healthy people, protein requirements are estimated at 0.8 g/kg/day. However, for patients with metabolic stress or kidney failure and for elderly patients, requirements may be higher (see

Table 3-1).

Assessing Response to Nutritional Support

There is no gold standard to assess response. Clinicians commonly use indicators of lean body mass such as the following:

• Body mass index (BMI)

• Body composition analysis

• Body fat distribution (see pp. 11 and 58)

Nitrogen balance, response to skin antigens, muscle strength measurement, and indirect calorimetry can also be used.

[**Table 3-1.** Estimated Adult Daily Protein Requirement]

Nitrogen balance, which reflects the balance between protein needs and supplies, is the difference between amount of nitrogen ingested and amount lost. A positive balance (ie, more ingested than lost) implies adequate intake. Precise measurement is impractical, but estimates help assess response to nutritional support. Nitrogen intake is estimated from protein intake: nitrogen (g) equals protein (g)/6.25. Estimated nitrogen losses consist of urinary nitrogen losses (estimated by measuring urea nitrogen content of an accurately obtained 24-h urine collection) plus stool losses (estimated at 1 g/day if stool is produced; negligible if stool is not produced) plus insensible and other unmeasured losses (estimated at 3 g).

Response to skin antigens, a measure of delayed hypersensitivity, often increases to normal as undernourished patients respond to nutritional support. However, other factors can affect response to skin antigens.

Muscle strength indirectly reflects increases in lean body mass. It can be measured quantitatively, by hand-grip dynamometry, or electrophysiologically (typically by stimulating the ulnar nerve with an electrode).

Levels of acute-phase reactant serum proteins (particularly short-lived proteins such as prealbumin [transthyretin], retinol-binding protein, and transferrin) sometimes correlate with improved nutritional status, but these levels correlate better with inflammatory conditions.

Enteral Tube Nutrition

Enteral tube nutrition is indicated for patients who have a functioning GI tract but cannot ingest enough nutrients orally because they are unable or unwilling to take oral feedings. Compared with parenteral nutrition, enteral nutrition has the following advantages:

• Better preservation of the structure and function of the GI tract

• Lower cost

• Probably fewer complications, particularly infections

Specific indications for enteral nutrition include the following:

• Prolonged anorexia

• Severe protein-energy undernutrition

• Coma or depressed sensorium

• Liver failure

• Inability to take oral feedings due to head or neck trauma or neurologic disorders

• Critical illnesses (eg, burns) causing metabolic stress

Other indications may include bowel preparation for surgery in seriously ill or undernourished patients, closure of enterocutaneous fistulas, and small-bowel adaptation after massive intestinal resection or in disorders that may cause malabsorption (eg, Crohn's disease).

Procedure: If tube feeding is needed for ≤ 4 to 6 wk, a small-caliber, soft nasogastric or nasoenteric (eg, nasoduodenal) tube made of silicone or polyurethane is usually used. If a nasal injury or deformity makes nasal placement difficult, an orogastric or other oroenteric tube can be placed.

Tube feeding for > 4 to 6 wk usually requires a gastrostomy or jejunostomy tube, placed endoscopically, surgically, or radiologically. Choice depends on physician capabilities and patient preference.

Jejunostomy tubes are useful for patients with contraindications to gastrostomy (eg, gastrectomy, bowel obstruction proximal to the jejunum). However, these tubes do not pose less risk of tracheobronchial aspiration than gastrostomy tubes, as is often thought. Jejunostomy tubes are easily dislodged and are usually used only for inpatients.

Feeding tubes are surgically placed if endoscopic and radiologic placement is unavailable, technically impossible, or unsafe (eg, because of overlying bowel). Open or laparoscopic techniques can be used.

Formulas: Liquid formulas commonly used include feeding modules and polymeric or other specialized formulas.

Feeding modules are commercially available products that contain a single nutrient, such as proteins, fats, or carbohydrates. Feeding modules may be used individually to treat a specific deficiency or combined with other formulas to completely satisfy nutritional requirements.

Polymeric formulas (including blenderized food and milk-based or lactose-free commercial formulas) are commercially available and generally provide a complete, balanced diet. For oral or tube feedings, they are usually preferred to feeding modules. In hospitalized patients, lactose-free formulas are the most commonly used polymeric formulas. However, milk-based formulas tend to taste better than lactose-free formulas. Patients with lactose intolerance may be able to tolerate milk-based formulas given slowly by continuous infusion.

Specialized formulas include hydrolyzed protein or sometimes amino acid formulas, which are used for patients who have difficulty digesting complex proteins. However, these formulas are expensive and usually unnecessary. Most patients with pancreatic insufficiency, if given enzymes, and most patients with malabsorption can digest complex proteins. Other specialized formulas (eg, calorie- and protein-dense formulas for patients whose fluids are restricted, fiber-enriched formulas for constipated patients) may be helpful.

Administration: Patients should be sitting upright at 30 to 45° during tube feeding and for 1 to 2 h afterward to minimize incidence of nosocomial aspiration pneumonia and to allow gravity to help propel the food. Tube feedings are given in boluses several times a day or by continuous infusion. Bolus feeding is more physiologic and may be preferred for patients with diabetes. Continuous infusion is necessary if boluses cause nausea.

[
Table 3-2. Complications of Enteral Tube Nutrition]

For bolus feeding, total daily volume is divided into 4 to 6 separate feedings, which are injected through

the tube with a syringe or infused by gravity from an elevated bag. After feedings, the tube is flushed with water to prevent clogging.

Nasogastric or nasoduodenal tube feeding often causes diarrhea initially; thus, feedings are usually started with small amounts of dilute preparations and increased as tolerated. Most formulas contain 0.5, 1, or 2 kcal/mL. Formulas with higher caloric concentration (less water per calorie) may cause decreased gastric emptying and thus higher gastric residuals than when more dilute formulas with the same number of calories are used. Initially, a 1-kcal/mL commercially prepared solution may be given undiluted at 50 mL/h or, if patients have not been fed for a while, at 25 mL/h. Usually, these solutions do not supply enough water, particularly if vomiting, diarrhea, sweating, or fever has increased water loss. Extra water is supplied as boluses via the feeding tube or IV. After a few days, the rate or concentration can be increased as needed to meet caloric and water needs.

Jejunostomy tube feeding requires greater dilution and smaller volumes. Feeding usually begins at a concentration of ≤ 0.5 kcal/mL and a rate of 25 mL/h. After a few days, concentrations and volumes can be increased to eventually meet caloric and water needs. Usually, the maximum that can be tolerated is 0.8 kcal/mL at 125 mL/h, providing 2400 kcal/day.

Complications: Complications are common and can be serious (see Table 3-2).

Total Parenteral Nutrition

Parenteral nutrition is by definition given IV.

Partial parenteral nutrition supplies only part of daily nutritional requirements, supplementing oral intake. Many hospitalized patients are given dextrose or amino acid solutions by this method.

Total parenteral nutrition (TPN) supplies all daily nutritional requirements. TPN can be used in the hospital or at home. Because TPN solutions are concentrated and can cause thrombosis of peripheral veins, a central venous catheter is usually required.

Parenteral nutrition should not be used routinely in patients with an intact GI tract. Compared with enteral nutrition, it causes more complications, does not preserve GI tract structure and function as well, and is more expensive.

Indications: TPN may be the only feasible option for patients who do not have a functioning GI tract or who have disorders requiring complete bowel rest, such as the following:

• Some stages of Crohn's disease or ulcerative colitis

• Bowel obstruction

• Certain pediatric GI disorders (eg, congenital GI anomalies, prolonged diarrhea regardless of its cause)

• Short bowel syndrome due to surgery

Nutritional content: TPN requires water (30 to 40 mL/kg/day), energy (30 to 60 kcal/kg/day, depending on energy expenditure), amino acids (1 to 2.0 g/kg/day, depending on the degree of catabolism), essential fatty acids, vitamins, and minerals (see Table 3-3). Children who need TPN may have different fluid requirements and need more energy (up to 120 kcal/kg/day) and amino acids (up to 2.5 or 3.5 g/kg/day).

Basic TPN solutions are prepared using sterile techniques, usually in liter batches according to standard formulas. Normally, 2 L/day of the standard solution is needed. Solutions may be modified based on laboratory results, underlying disorders, hypermetabolism, or other factors.

Most calories are supplied as carbohydrate. Typically, about 4 to 5 mg/kg/day of dextrose is given. Standard solutions contain up to about 25% dextrose, but the amount and concentration depend on other

factors, such as metabolic needs and the proportion of caloric needs that are supplied by lipids. Commercially available lipid emulsions are often added to supply essential fatty acids and triglycerides; 20 to 30% of total calories are usually supplied as lipids. However, withholding lipids and their calories may help obese patients mobilize endogenous fat stores, increasing insulin sensitivity.

Solutions: Many solutions are commonly used. Electrolytes can be added to meet the patient's needs.

Solutions vary depending on other disorders present and patient age, as for the following:

- For renal insufficiency not being treated with dialysis or for liver failure: Reduced protein content and a high percentage of essential amino acids
- For heart or kidney failure: Limited volume (liquid) intake
- For respiratory failure: A lipid emulsion that provides most of nonprotein calories to minimize CO_2 production by carbohydrate metabolism
- For neonates: Lower dextrose concentrations (17 to 18%)

Beginning TPN administration: Because the central venous catheter needs to remain in place for a long time, strict sterile technique must be used during insertion and maintenance. The TPN line should not be used for any other purpose. External tubing should be changed every 24 h with the first bag of the day. In-line filters have not been shown to decrease complications. Dressings should be kept sterile and are usually changed every 48 h using strict sterile techniques. If TPN is given outside the hospital, patients must be taught to recognize symptoms of infection, and qualified home nursing must be arranged.

The solution is started slowly at 50% of the calculated requirements, using 5% dextrose to make up the balance of fluid requirements. Energy and nitrogen should be given simultaneously. The amount of regular insulin given (added directly to the TPN solution) depends on the plasma glucose level; if the level is normal and the final solution contains 25% dextrose, the usual starting dose is 5 to 10 units of regular insulin/L of TPN fluid.

Monitoring: Progress should be followed on a flowchart. An interdisciplinary nutrition team, if available, should monitor patients. Weight, CBC, electrolytes, and BUN should be monitored often (eg, daily for inpatients). Plasma glucose should be monitored every 6 h until patients and glucose levels become stable. Fluid intake and output should be monitored continuously. When patients become stable, blood tests can be done much less often.

Liver function tests should be done. Plasma proteins (eg, serum albumin, possibly transthyretin or retinol-binding protein), PT, plasma and urine osmolality, and Ca, Mg, and phosphate should be measured twice/wk. Changes in transthyretin and retinol-binding protein reflect overall clinical status rather than nutritional status alone. If possible, blood tests should not be done during glucose infusion. Full nutritional assessment (including BMI calculation and anthropometric measurements—see pp. 11 and 58) should be repeated at 2-wk intervals.

Complications: About 5 to 10% of patients have complications related to central venous access.

[**Table 3-3.** Basic Adult Daily Requirements for Total Parenteral Nutrition]

Catheter-related sepsis occurs in about ≥ 50% of patients. Glucose abnormalities (hyperglycemia or hypoglycemia) or liver dysfunction occurs in > 90% of patients.

Glucose abnormalities are common. Hyperglycemia can be avoided by monitoring plasma glucose often, adjusting the insulin dose in the TPN solution and giving subcutaneous insulin as needed. Hypoglycemia can be precipitated by suddenly stopping constant concentrated dextrose infusions. Treatment depends on the degree of hypoglycemia. Short-term hypoglycemia may be reversed with 50% dextrose IV; more prolonged hypoglycemia may require infusion of 5 or 10% dextrose for 24 h before

resuming TPN via the central venous catheter.

Hepatic complications include liver dysfunction, painful hepatomegaly, and hyperammonemia. They can develop at any age but are most common among infants, particularly premature ones (whose liver is immature).

- Liver dysfunction may be transient, evidenced by increased transaminases, bilirubin, and alkaline phosphatase; it commonly occurs when TPN is started. Delayed or persistent elevations may result from excess amino acids. Pathogenesis is unknown, but cholestasis and inflammation may contribute. Progressive fibrosis occasionally develops. Reducing protein delivery may help.

- Painful hepatomegaly suggests fat accumulation; carbohydrate delivery should be reduced.

- Hyperammonemia can develop in infants, causing lethargy, twitching, and generalized seizures. Arginine supplementation at 0.5 to 1.0 mmol/kg/day can correct it.

If infants develop any hepatic complication, limiting amino acids to 1.0 g/kg/day may be necessary.

Abnormalities of serum electrolytes and minerals should be corrected by modifying subsequent infusions or, if correction is urgently required, by beginning appropriate peripheral vein infusions. Vitamin and mineral deficiencies are rare when solutions are given correctly. Elevated BUN may reflect dehydration, which can be corrected by giving free water as 5% dextrose via a peripheral vein.

Volume overload (suggested by > 1 kg/day weight gain) may occur when patients have high daily energy requirements and thus require large fluid volumes.

Metabolic bone disease, or bone demineralization (osteoporosis or osteomalacia), develops in some patients given TPN for > 3 mo. The mechanism is unknown. Advanced disease can cause severe periarticular, lower-extremity, and back pain. Temporarily or permanently stopping TPN is the only known treatment.

Adverse reactions to lipid emulsions (eg, dyspnea, cutaneous allergic reactions, nausea, headache, back pain, sweating, dizziness) are uncommon but may occur early, particularly if lipids are given at > 1.0 kcal/kg/h. Temporary hyperlipidemia may occur, particularly in patients with kidney or liver failure; treatment is usually not required. Delayed adverse reactions to lipid emulsions include hepatomegaly, mild elevation of liver enzymes, splenomegaly, thrombocytopenia, leukopenia, and, especially in premature infants with respiratory distress syndrome, pulmonary function abnormalities. Temporarily or permanently slowing or stopping lipid emulsion infusion may prevent or minimize these adverse reactions.

Gallbladder complications include cholelithiasis, gallbladder sludge, and cholecystitis. These complications can be caused or worsened by prolonged gallbladder stasis. Stimulating contraction by providing about 20 to 30% of calories as fat and stopping glucose infusion several hours a day is helpful. Oral or enteral intake also helps. Treatment with metronidazole, ursodeoxycholic acid, phenobarbital, or cholecystokinin helps some patients with cholestasis.

Nutritional Support for Dying or Severely Demented Patients

Anorexia or loss of appetite is common among dying patients (see p. 3485). Behavioral measures (eg, using flexible feeding schedules, feeding slowly, giving small portions or favorite or strongly flavored foods) can often increase oral intake. A small amount of a favorite alcoholic drink, given 30 min before meals, may also help. Certain antidepressants, megestrol acetate, and dronabinol may stimulate appetite. Metoclopramide enhances gastric emptying, but it may take 1 to 2 wk to reach peak effectiveness.

Advanced dementia eventually leads to inability to eat; sometimes affected patients are given tube feedings. However, there is no convincing evidence that tube feedings prolong life, provide comfort, improve function, or prevent complications (eg, aspiration, pressure ulcers).

Tube feedings and parenteral nutrition cause discomfort and are usually not indicated for patients who

are dying or too demented to eat. Forgoing nutritional support may be difficult for family members to accept, but they should understand that patients are usually more comfortable eating and drinking as they choose. Sips of water and easy-to-swallow foods may be useful. Supportive care, including good oral hygiene (eg, brushing the teeth, moistening the oral cavity with swabs and ice chips as needed, applying lip salve), can physically and psychologically comfort the patients and the family members who provide the care.

Counseling may help family members who are dealing with anxieties about whether to use invasive nutritional support.

Chapter 4. Vitamin Deficiency, Dependency, and Toxicity

Introduction

Vitamins may be fat soluble (vitamins A, D, E, and K) or water soluble (B vitamins and vitamin C). The B vitamins include biotin, folate, niacin, pantothenic acid, riboflavin (B_2), thiamin (B_1), B_6 (eg, pyridoxine), and B_{12} (cobalamins). For dietary requirements, sources, functions, effects of deficiencies and toxicities, blood levels, and usual therapeutic dosages for vitamins, see Tables 4-1 and 4-2.

Dietary requirements for vitamins (and other nutrients) are expressed as daily recommended intake (DRI). There are 3 types of DRI:

- **Recommended daily allowance (RDA):** RDAs are set to meet the needs of 97 to 98% of healthy people.
- **Adequate intake (AI):** When data to calculate an RDA are insufficient, AIs are based on observed or experimentally determined estimates of nutrient intake by healthy people.
- **Tolerable upper intake level (UL):** ULs are the largest amount of a nutrient that most adults can ingest daily without risk of adverse health effects.

In developed countries, vitamin deficiencies result mainly from poverty, food faddism, drugs (see p. 7 and Table 4-3), alcoholism, or prolonged and inadequately supplemented parenteral feeding. Mild vitamin deficiency is common among frail and institutionalized elderly people who have protein-energy undernutrition. In developing countries, deficiencies can result from lack of access to nutrients. Deficiencies of water-soluble vitamins (except vitamin B_{12}) may develop after weeks to months of undernutrition. Deficiencies of fat-soluble vitamins and of vitamin B_{12} take > 1 yr to develop because the body stores them in relatively large amounts. Intake of vitamins sufficient to prevent classic vitamin deficiencies (like scurvy or beriberi) may not be adequate for optimum health. This area remains one of controversy and active research.

Vitamin dependency results from a genetic defect involving metabolism of a vitamin. In some cases, vitamin doses as high as 1000 times the DRI improve function of the altered metabolic pathway. Vitamin toxicity (hypervitaminosis) usually results from taking megadoses of vitamin A, D, C, B_6, or niacin.

Because many people eat irregularly, foods alone may provide suboptimal amounts of some vitamins. In these cases, the risk of certain cancers or other disorders may be increased. Because of this risk, routine daily multivitamin supplements are sometimes recommended.

Biotin and Pantothenic Acid

Biotin acts as a coenzyme for carboxylation reactions essential to fat and carbohydrate metabolism. Adequate intake for adults is 30 µg/day. Pantothenic acid is widely distributed in foods; it is an essential component of coenzyme A. Adults probably require about 5 mg/day. A beneficial role for pantothenic acid supplementation in lipid metabolism, RA, or athletic performance remains unproved. Isolated deficiency of biotin or pantothenic acid virtually never occurs.

Folate

Folate (folic acid) is now added to enriched grain foods in the US. Folate is also plentiful in various plant foods and meats, but its bioavailability is greater when it is in supplements

[**Table 4-1.** Recommended Daily Intakes for Vitamins]

or enriched foods than when it occurs naturally in food.

Folates are involved in RBC maturation and synthesis of purines and pyrimidines. They are required for development of the fetal nervous system. Absorption occurs in the duodenum and upper jejunum. Enterohepatic circulation of folate occurs. Folate supplements

[**Table 4-2.** Sources, Functions, and Effects of Vitamins]

do not protect against coronary artery disease or stroke (by lowering homocysteine levels); their role in reducing the risk of various cancers is unclear. The upper limit for folate intake is 1000 µg; higher doses (up to 5 mg) are recommended for women who have had a baby with a neural tube defect. Folate is essentially nontoxic.

Folate Deficiency

Folate deficiency is common. It may result from inadequate intake, malabsorption, or use of various drugs. Deficiency causes megaloblastic anemia (indistinguishable from that due to vitamin B_{12} deficiency). Maternal deficiency increases the risk of neural tube birth defects. Diagnosis requires laboratory testing to confirm. Measurement of neutrophil hypersegmentation is sensitive and readily available. Treatment with oral folate is usually successful.

Etiology and Pathophysiology

The most common causes are inadequate intake (usually in patients with undernutrition or alcoholism), increased demand (eg, due to pregnancy or breastfeeding), and impaired absorption (eg, in tropical sprue, due to certain drugs). Deficiency can also result from inadequate bioavailability and increased excretion (see
Table 4-4).

Prolonged cooking destroys folate, predisposing to inadequate intake. Intake is sometimes barely adequate (eg, in alcoholics). Liver stores provide only a several-month supply.

Alcohol interferes with folate absorption, metabolism, renal excretion, and enterohepatic reabsorption, as well as intake. 5-Fluorouracil, metformin, methotrexate, phenobarbital, phenytoin, sulfasalazine, triamterene, and trimethoprim impair folate metabolism.

In the US, many dietary staples (eg, cereals, grain products) are routinely enriched with folate, tending to reduce risk of deficiency.

[**Table 4-3.** Potential Vitamin-Drug Interactions]

Symptoms and Signs

Folate deficiency may cause glossitis, diarrhea, depression, and confusion. Anemia may develop insidiously and, because of compensatory mechanisms, be more severe than symptoms suggest.

Folate deficiency during pregnancy increases the risk of fetal neural tube defects and perhaps other brain defects (see p. 2992).

Diagnosis

• CBC and serum vitamin B_{12} and folate levels

CBC may indicate megaloblastic anemia indistinguishable from that of vitamin B_{12} deficiency. If serum folate is < 3 µg/L or ng/mL (< 7 nmol/L), deficiency is likely. Serum folate reflects folate status unless intake has recently increased or decreased. If intake has changed, erythrocyte (RBC) folate level better reflects tissue stores. A level of < 140 µg/L or ng/mL (< 305 nmol/L) indicates inadequate status. Also, an increase in the homocysteine level suggests tissue folate deficiency (but the level is also affected by

vitamin B_{12} and vitamin B_6 levels, renal insufficiency, and genetic factors). A normal methylmalonic acid (MMA) level may differentiate folate deficiency from vitamin B_{12} deficiency because MMA levels rise in vitamin B_{12} deficiency but not in folate deficiency.

Treatment

• Supplemental oral folate

Folate 400 to 1000 µg po once/day replenishes tissues and is usually successful even if deficiency has resulted from malabsorption. The normal requirement is 400 µg/day.

[Table 4-4. Causes of Folate Deficiency]

(CAUTION: *In patients with megaloblastic anemia, vitamin B_{12} deficiency must be ruled out before treating with folate. If vitamin B_{12} deficiency is present, folate supplementation can alleviate the anemia but does not reverse and may even worsen neurologic deficits.*) For pregnant women, the recommended daily allowance (RDA) is 600 µg/day. For women who have had a fetus or infant with a neural tube defect, the recommended dose is 1000 to 5000 µg/day.

Niacin

Niacin (nicotinic acid, nicotinamide) derivatives include nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are coenzymes in oxidation-reduction reactions. They are vital in cell metabolism. Because dietary tryptophan can be metabolized to niacin, foods rich in tryptophan (eg, dairy products) can compensate for inadequate dietary niacin.

Niacin Deficiency

Dietary niacin deficiency (causing pellagra) is uncommon in developed countries. Clinical manifestations include the "three Ds": localized pigmented rash (dermatitis); gastroenteritis (diarrhea); and widespread neurologic deficits, including cognitive decline (dementia). Diagnosis is usually clinical, and dietary supplementation (oral or, if needed, IM) is usually successful.

Etiology

Primary deficiency results from extremely inadequate intake of both niacin and tryptophan, which usually occurs in areas where maize (Indian corn) constitutes a substantial part of the diet. Bound niacin, found in maize, is not assimilated in the GI tract unless it has been previously treated with alkali, as when tortillas are prepared. Corn protein is also deficient in tryptophan. The high incidence of pellagra in India among people who eat millet with a high leucine content has led to the hypothesis that amino acid imbalance may contribute to deficiency. Deficiencies of protein and many B vitamins commonly accompany primary niacin deficiency.

Secondary deficiency may be due to diarrhea, cirrhosis, or alcoholism. Pellagra also may occur in carcinoid syndrome (tryptophan is diverted to form 5-hydroxytryptophan and serotonin) and in Hartnup disease (absorption of tryptophan by the intestine and kidneys is defective).

Symptoms and Signs

Pellagra is characterized by skin, mucous membrane, CNS, and GI symptoms. Advanced pellagra can cause a symmetric photosensitive rash, stomatitis, glossitis, diarrhea, and mental aberrations. Symptoms may appear alone or in combination.

Skin symptoms include several types of lesions, which are usually bilaterally symmetric. The distribution of lesions—at pressure points or sun-exposed skin—is more pathognomonic than the form of the lesions. Lesions can develop in a glovelike distribution on the hands (pellagrous glove) or in a boot-shaped

distribution on the feet and legs (pellagrous boot). Sunlight causes Casal's necklace and butterfly-shaped lesions on the face.

Mucous membrane symptoms affect primarily the mouth but may also affect the vagina and urethra. Glossitis and stomatitis characterize acute deficiency. As the deficiency progresses, the tongue and oral mucous membranes become reddened, followed by pain in the mouth, increased salivation, and edema of the tongue. Ulcerations may appear, especially under the tongue, on the mucosa of the lower lip, and opposite the molar teeth.

GI symptoms early in the deficiency include burning in the pharynx and esophagus and abdominal discomfort and distention. Constipation is common. Later, nausea, vomiting, and diarrhea may occur. Diarrhea is often bloody because of bowel hyperemia and ulceration.

CNS symptoms include psychosis, encephalopathy (characterized by impaired consciousness), and cognitive decline (dementia). Psychosis is characterized by memory impairment, disorientation, confusion, and confabulation; the predominant symptom may be excitement, depression, mania, delirium, or paranoia.

Diagnosis

• Clinical evaluation

Diagnosis is clinical and may be straightforward when skin and mouth lesions, diarrhea, delirium, and dementia occur simultaneously. More often, the presentation is not so specific. Differentiating the CNS changes from those in thiamin deficiency is difficult. A history of a diet lacking niacin and tryptophan may help establish the diagnosis. A favorable response to treatment with niacin can usually confirm it. If available, laboratory testing can help confirm the diagnosis, particularly when the diagnosis is otherwise unclear. Urinary excretion of N^1-methylnicotinamide (NMN) is decreased; < 0.8 mg/day (< 5.8 µmol/day) suggests a niacin deficiency.

Treatment

• Nicotinamide and other nutrients

Because multiple deficiencies are common, a balanced diet, including other B vitamins (particularly riboflavin and pyridoxine), is needed. Nicotinamide is usually used to treat deficiency, because nicotinamide, unlike nicotinic acid (the most common form of niacin), does not cause flushing, itching, burning, or tingling sensations. Nicotinamide is given in doses ranging from 40 to 250 mg/day po in divided doses 3 to 4 times a day.

Niacin Toxicity

Niacin (nicotinic acid) in large amounts is sometimes used to lower low-density lipoprotein (LDL) cholesterol and triglyceride levels and to increase high-density lipoprotein (HDL) cholesterol levels. Symptoms may include flushing and, rarely, hepatotoxicity.

Immediate- and sustained-release preparations of niacin (but not nicotinamide) may improve lipid levels. Flushing, which is prostaglandin-mediated, is more common with immediate-release preparations. It may be more intense after alcohol ingestion, aerobic activity, sun exposure, and consumption of spicy foods. Flushing is minimized if niacin is taken after meals or if aspirin (325 mg) is taken 30 to 45 min before niacin. The chance of severe flushing can be reduced by starting immediate-release niacin at a low dose (eg, 50 mg tid) and increasing it very slowly. At intermediate doses (1000 mg/day), triglyceride levels decrease 15 to 20%, and HDL cholesterol levels increase 15 to 30%. Reductions in LDL cholesterol are modest (< 10%). Higher doses of niacin (3000 mg/day) reduce LDL cholesterol 15 to 20% but may cause jaundice, abdominal discomfort, blurred vision, worsening of hyperglycemia, and precipitation of preexisting gout. People with a liver disorder probably should not take high-dose niacin.

Hepatotoxicity may be more common with some sustained-release preparations. Some authorities

recommend checking levels of uric acid, serum glucose, and plasma transaminases every 6 to 8 wk until the dose of niacin has been stabilized.

Riboflavin

Riboflavin (vitamin B_2) is involved in carbohydrate metabolism as an essential coenzyme in many oxidation-reduction reactions. Riboflavin is essentially nontoxic.

Riboflavin Deficiency

Riboflavin deficiency usually occurs with other B-vitamin deficiencies. Symptoms and signs include sore throat, lesions of the lips and mucosa of the mouth, glossitis, conjunctivitis, seborrheic dermatitis, and normochromicnormocytic anemia. Diagnosis is usually clinical. Treatment consists of oral or, if needed, IM riboflavin.

Primary riboflavin deficiency results from inadequate intake of fortified cereals, milk, and other animal products. The most common causes of secondary deficiency are chronic diarrhea, malabsorption syndromes, liver disorders, hemodialysis, peritoneal dialysis, long-term use of barbiturates, and chronic alcoholism.

Symptoms and Signs

The most common signs are pallor and maceration of the mucosa at the angles of the mouth (angular stomatitis) and vermilion surfaces of the lips (cheilosis), eventually replaced by superficial linear fissures. The fissures can become infected with *Candida albicans*, causing grayish white lesions (perleche). The tongue may appear magenta. Seborrheic dermatitis develops, usually affecting the nasolabial folds, ears, eyelids, and scrotum or labia majora. These areas become red, scaly, and greasy.

Rarely, neovascularization and keratitis of the cornea occur, causing lacrimation and photophobia.

Diagnosis

The lesions characteristic of riboflavin deficiency are nonspecific. Riboflavin deficiency should be suspected if characteristic signs develop in a patient with other B vitamin deficiencies. Diagnosis can be confirmed by a therapeutic trial or laboratory testing, usually by measuring urinary excretion of riboflavin.

Treatment

Riboflavin 5 to 10 mg/day po is given until recovery. Other water-soluble vitamins should also be given.

Thiamin

Thiamin (vitamin B_1) is widely available in the diet. Thiamin is involved in carbohydrate, fat, amino acid, glucose, and alcohol metabolism. Thiamin is essentially nontoxic.

Thiamin Deficiency

Thiamin deficiency (causing beriberi) is most common among people subsisting on white rice or highly refined carbohydrates in developing countries and among alcoholics. Symptoms include diffuse polyneuropathy, high-output heart failure, and Wernicke-Korsakoff syndrome. Thiamin is given to help diagnose and treat the deficiency.

Etiology

Primary thiamin deficiency is caused by inadequate intake of thiamin. It is commonly due to a diet of highly refined carbohydrates (eg, polished rice, white flour, white sugar). It also develops when intake of other nutrients is inadequate; it often occurs with other B vitamin deficiencies.

Secondary thiamin deficiency is caused by increased demand (eg, due to hyperthyroidism, pregnancy, breastfeeding, strenuous exercise, or fever), impaired absorption (eg, due to prolonged diarrhea), or impaired metabolism (eg, due to hepatic insufficiency). In alcoholics, many mechanisms contribute to thiamin deficiency; they include decreased intake, impaired absorption and use, increased demand, and possibly an apoenzyme defect.

Pathophysiology

Deficiency causes degeneration of peripheral nerves, thalamus, mammillary bodies, and cerebellum. Cerebral blood flow is markedly reduced, and vascular resistance is increased.

The heart may become dilated; muscle fibers become swollen, fragmented, and vacuolized, with interstitial spaces dilated by fluid. Vasodilation occurs and can result in edema in the feet and legs. Arteriovenous shunting of blood increases. Eventually, high-output heart failure may occur.

Symptoms and Signs

Early symptoms are nonspecific: fatigue, irritability, poor memory, sleep disturbances, precordial pain, anorexia, and abdominal discomfort.

Dry beriberi refers to peripheral neurologic deficits due to thiamin deficiency. These deficits are bilateral and roughly symmetric, occurring in a stocking-glove distribution. They affect predominantly the lower extremities, beginning with paresthesias in the toes, burning in the feet (particularly severe at night), muscle cramps in the calves, pains in the legs, and plantar dysesthesias. Calf muscle tenderness, difficulty rising from a squatting position, and decreased vibratory sensation in the toes are early signs. Muscle wasting occurs. Continued deficiency worsens polyneuropathy, which can eventually affect the arms.

Wernicke-Korsakoff syndrome, which combines Wernicke's encephalopathy (see p. 1522) and Korsakoff's psychosis (see p. 1523), occurs in some alcoholics who do not consume foods fortified with thiamin. Wernicke's encephalopathy consists of psychomotor slowing or apathy, nystagmus, ataxia, ophthalmoplegia, impaired consciousness, and, if untreated, coma and death. It probably results from severe acute deficiency superimposed on chronic deficiency. Korsakoff's psychosis consists of mental confusion, dysphonia, and confabulation with impaired memory of recent events. It probably results from chronic deficiency and may develop after repeated episodes of Wernicke's encephalopathy.

Cardiovascular (wet) beriberi is myocardial disease due to thiamin deficiency. The first effects are vasodilation, tachycardia, a wide pulse pressure, sweating, warm skin, and lactic acidosis. Later, heart failure develops, causing orthopnea and pulmonary and peripheral edema. Vasodilation can continue, sometimes resulting in shock.

Infantile beriberi occurs in infants (usually by age 3 to 4 wk) who are breastfed by thiamin-deficient mothers. Heart failure (which may occur suddenly), aphonia, and absent deep tendon reflexes are characteristic.

Because thiamin is necessary for glucose metabolism, glucose infusions may precipitate or worsen symptoms of deficiency in thiamin-deficient people.

Diagnosis

• Favorable response to thiamin

Diagnosis is usually based on a favorable response to treatment with thiamin in a patient with symptoms or signs of deficiency. Similar bilateral lower-extremity polyneuropathies due to other disorders (eg, diabetes, alcoholism, vitamin B_{12} deficiency, heavy metal poisoning) do not respond to thiamin. Single-nerve neuritides (mononeuropathies—eg, sciatica) and multiple mononeuropathies (mononeuritis multiplex) are unlikely to result from thiamin deficiency.

Electrolytes, including Mg, should be measured to exclude other causes. For confirmation in equivocal cases, erythrocyte transketolase activity and 24-h urinary thiamin excretion may be measured.

Diagnosis of cardiovascular beriberi can be difficult if other disorders that cause heart failure are present. A therapeutic trial of thiamin can help.

Treatment

• Supplemental thiamin, with dose based on clinical manifestations

Ensuring that dietary supplies of thiamin are adequate is important regardless of symptoms. Because IV glucose can worsen thiamin deficiency, alcoholics and others at risk of thiamin deficiency should receive IV thiamin 100 mg before receiving IV glucose solutions.

For mild polyneuropathy, thiamin 10 to 20 mg po once/day is given for 2 wk. For moderate or advanced neuropathy, the dose is 20 to 30 mg/day; it should be continued for several weeks after symptoms disappear. For edema and congestion due to cardiovascular beriberi, thiamin 100 mg IV once/day is given for several days. Heart failure is also treated.

For Wernicke-Korsakoff syndrome, thiamin 50 to 100 mg IM or IV bid must usually be given for several days, followed by 10 to 20 mg once/day until a therapeutic response is obtained. Anaphylactic reactions to IV thiamin are rare. Symptoms of ophthalmoplegia may resolve in a day; improvement in patients with Korsakoff psychosis may take 1 to 3 mo. Recovery from neurologic deficits is often incomplete in Wernicke-Korsakoff syndrome and in other forms of thiamin deficiency.

Because thiamin deficiency often occurs with other B vitamin deficiencies, multiple water-soluble vitamins are usually given for several weeks. Patients should continue to consume a nutritious diet, supplying 1 to 2 times the daily recommended intake of vitamins; all alcohol intake should stop.

Vitamin A

Vitamin A (retinol) is required for the formation of rhodopsin, a photoreceptor pigment in the retina. Vitamin A helps maintain epithelial tissues. Normally, the liver stores 80 to 90% of the body's vitamin A. To use vitamin A, the body releases it into the circulation bound to prealbumin (transthyretin) and retinol-binding protein. β-Carotene and other provitamin carotenoids, contained in green leafy and yellow vegetables and deep- or bright-colored fruits, are converted to vitamin A. Carotenoids are absorbed better from vegetables when they are cooked or homogenized and served with some fats or oils.

Retinol activity equivalents (RAE) were developed because provitamin A carotenoids have less vitamin A activity than preformed vitamin A; 1 µg retinol = 3.33 IU.

Synthetic vitamin analogs (retinoids) are being used increasingly in dermatology. The possible protective role of β-carotene, retinol, and retinoids against some epithelial cancers is under study. However, risk of certain cancers may be increased after β-carotene supplementation.

Vitamin A Deficiency

Vitamin A deficiency can result from inadequate intake, fat malabsorption, or liver disorders. Deficiency impairs immunity and hematopoiesis and causes rashes and typical ocular effects (eg, xerophthalmia, night blindness). Diagnosis is based on typical ocular findings and low vitamin A levels. Treatment consists of vitamin A given orally or, if symptoms are severe or malabsorption is the cause, parenterally.

Etiology

Primary vitamin A deficiency is usually caused by prolonged dietary deprivation. It is endemic in areas such as southern and eastern Asia, where rice, devoid of β-carotene, is the staple food. Xerophthalmia due to primary deficiency is a common cause of blindness among young children in developing countries.

Secondary vitamin A deficiency may be due to decreased bioavailability of provitamin A carotenoids or to interference with absorption, storage, or transport of vitamin A. Interference with absorption or storage is likely in sprue, cystic fibrosis, pancreatic insufficiency, duodenal bypass, chronic diarrhea, bile duct obstruction, giardiasis, and cirrhosis. Vitamin A deficiency is common in prolonged protein-energy undernutrition not only because the diet is deficient but also because vitamin A storage and transport is defective. In children with complicated measles, vitamin A can shorten the duration of the disorder and reduce the severity of symptoms and risk of death.

Symptoms and Signs

Impaired dark adaptation of the eyes, which can lead to night blindness, is an early symptom. Xerophthalmia (which is nearly pathognomonic) results from keratinization of the eyes. It involves drying (xerosis) and thickening of the conjunctivae and corneas. Superficial foamy patches composed of epithelial debris and secretions on the exposed bulbar conjunctiva (Bitot's spots) develop. In advanced deficiency, the cornea becomes hazy and can develop erosions, which can lead to its destruction (keratomalacia).

Keratinization of the skin and of the mucous membranes in the respiratory, GI, and urinary tracts can occur. Drying, scaling, and follicular thickening of the skin and respiratory infections can result. Immunity is generally impaired.

The younger the patient, the more severe are the effects of vitamin A deficiency. Growth retardation and infections are common among children. Mortality rate can exceed 50% in children with severe vitamin A deficiency.

Diagnosis

• Serum retinol levels, clinical evaluation, and response to vitamin A

Ocular findings suggest the diagnosis. Dark adaptation can be impaired in other disorders (eg, zinc deficiency, retinitis pigmentosa, severe refractive errors, cataracts, diabetic retinopathy). If dark adaptation is impaired, rod scotometry and electroretinography are done to determine whether vitamin A deficiency is the cause.

Serum levels of retinol are measured. Normal range is 28 to 86 µg/dL (1 to 3 µmol/L). However, levels decrease only after the deficiency is advanced because the liver contains large stores of vitamin A. Also, decreased levels may result from acute infection, which causes retinol-binding protein and transthyretin (also called prealbumin) levels to decrease transiently. A therapeutic trial of vitamin A may help confirm the diagnosis.

Prevention

The diet should include dark green leafy vegetables, deep- or bright-colored fruits (eg, papayas, oranges), carrots, and yellow vegetables (eg, squash, pumpkin). Vitamin A-fortified milk and cereals, liver, egg yolks, and fish liver oils are helpful. Carotenoids are absorbed better when consumed with some dietary fat. If milk allergy is suspected in infants, they should be given adequate vitamin A in formula feedings. In developing countries, prophylactic supplements of vitamin A palmitate in oil 60,000 RAE (200,000 IU) po every 6 mo are advised for all children between 1 and 5 yr of age; infants < 6 mo can be given a one-time dose of 15,000 RAE (50,000 IU), and those aged 6 to 12 mo can be given a one-time dose of 30,000 RAE (100,000 IU).

Treatment

• Vitamin A palmitate

Dietary deficiency is traditionally treated with vitamin A palmitate in oil 60,000 IU po once/day for 2 days, followed by 4500 IU po once/day. If vomiting or malabsorption is present or xerophthalmia is probable, a

dose of 50,000 IU for infants < 6 mo, 100,000 IU for infants 6 to 12 mo, or 200,000 IU for children > 12 mo and adults should be given for 2 days, with a third dose at least 2 wk later. The same doses are recommended for infants and children with complicated measles. Infants born of HIV-positive mothers should receive 50,000 IU (15,000 RAE) within 48 h of birth. Prolonged daily administration of large doses, especially to infants, must be avoided because toxicity may result.

For pregnant or breastfeeding women, prophylactic or therapeutic doses should not exceed 10,000 IU (3000 RAE)/day to avoid possible damage to the fetus or infant.

Vitamin A Toxicity

Vitamin A toxicity can be acute (usually due to accidental ingestion by children) or chronic. Both types usually cause headache and increased intracranial pressure. Acute toxicity also causes nausea and vomiting. Chronic toxicity also causes changes in skin, hair, and nails; abnormal liver test results; and, in a fetus, birth defects. Diagnosis is usually clinical. Unless birth defects are present, adjusting the dose almost always leads to complete recovery.

Acute vitamin A toxicity in children may result from taking large doses (> 100,000 RAE [> 300,000 IU]), usually accidentally. In adults, acute toxicity has occurred when arctic explorers ingested polar bear or seal livers, which contain several million units of vitamin A.

Chronic toxicity in older children and adults usually develops after doses of > 30,000 RAE (> 100,000 IU)/day have been taken for months. Megavitamin therapy is a possible cause, as are massive daily doses (50,000 to 120,000 RAE [150,000 to 350,000 IU]) of vitamin A or its metabolites, which are sometimes given for nodular acne or other skin disorders. Adults who consume > 1500 RAE (> 4500 IU)/day of vitamin A may develop osteoporosis. Infants who are given excessive doses (6,000 to 20,000 RAE [18,000 to 60,000 IU]/day) of water-miscible vitamin A may develop toxicity within a few weeks. Birth defects occur in children of women receiving isotretinoin (which is related to vitamin A) for acne treatment during pregnancy.

Although carotene is converted to vitamin A in the body, excessive ingestion of carotene causes carotenemia, not vitamin A toxicity. Carotenemia is usually asymptomatic but may lead to carotenodermia, in which the skin becomes yellow. When taken as a supplement, β-carotene has been associated with increased cancer risk; risk does not seem to increase when carotenoids are consumed in fruits and vegetables.

Symptoms and Signs

Although symptoms may vary, headache and rash usually develop during acute or chronic toxicity. Acute toxicity causes increased intracranial pressure. Drowsiness, irritability, abdominal pain, nausea, and vomiting are common. Sometimes the skin subsequently peels.

Early symptoms of chronic toxicity are sparsely distributed, coarse hair; alopecia of the eyebrows; dry, rough skin; dry eyes; and cracked lips. Later, severe headache, pseudotumor cerebri, and generalized weakness develop. Cortical hyperostosis of bone and arthralgia may occur, especially in children. Fractures may occur easily, especially in the elderly. In children, toxicity can cause pruritus, anorexia, and failure to thrive. Hepatomegaly and splenomegaly may occur.

In carotenodermia, the skin (but not the sclera) becomes deep yellow, especially on the palms and soles.

Diagnosis

• Clinical evaluation

Diagnosis is clinical. Blood vitamin levels correlate poorly with toxicity. However, if clinical diagnosis is equivocal, laboratory testing may help. In vitamin A toxicity, fasting serum retinol levels may increase from normal (28 to 86 µg/dL [1 to 3 µmol/L]) to > 100 µg/dL (> 3.49 µmol/L), sometimes to > 2000 µg/dL (> 69.8 µmol/L). Hypercalcemia is common.

Differentiating vitamin A toxicity from other disorders may be difficult. Carotenodermia may also occur in severe hypothyroidism and anorexia nervosa, possibly because carotene is converted to vitamin A more slowly.

Prognosis

Complete recovery usually occurs if vitamin A ingestion stops. Symptoms and signs of chronic toxicity usually disappear within 1 to 4 wk. However, birth defects in the fetus of a mother who has taken megadoses of vitamin A are not reversible.

Treatment

Vitamin A is stopped.

Vitamin B_6

Vitamin B_6 includes a group of closely related compounds: pyridoxine, pyridoxal, and pyridoxamine. They are metabolized in the body to pyridoxal phosphate, which acts as a coenzyme in many important reactions in blood, CNS, and skin metabolism. Vitamin B_6 is important in heme and nucleic acid biosynthesis and in lipid, carbohydrate, and amino acid metabolism.

Vitamin B_6 Deficiency and Dependency

Because vitamin B_6 is present in most foods, dietary deficiency is rare. Secondary deficiency may result from various conditions. Symptoms can include peripheral neuropathy, a pellagra-like syndrome, anemia, and seizures, which, particularly in infants, may not resolve when treated with anticonvulsants. Impaired metabolism (dependency) is rare; it causes various symptoms, including seizures, intellectual disability, and anemia. Diagnosis is usually clinical; no laboratory test readily assesses vitamin B_6 status. Treatment consists of giving oral vitamin B_6 and, when possible, treating the cause.

Dietary deficiency, though rare, can develop because extensive processing can deplete foods of vitamin B_6. Secondary deficiency most often results from protein-energy undernutrition, malabsorption, alcoholism, use of pyridoxine-inactivating drugs (eg, anticonvulsants, isoniazid, cycloserine, hydralazine, corticosteroids, penicillamine), or excessive loss. Rarely, it results from increased metabolic demand (eg, in hyperthyroidism).

Rare inborn errors of metabolism can affect pyridoxine metabolism.

The role of vitamin B_6 deficiency in increasing plasma homocysteine levels and in contributing to vascular disorders is under study.

Symptoms and Signs

Deficiency causes a pellagra-like syndrome, with seborrheic dermatitis, glossitis, and cheilosis, and, in adults, can cause depression, confusion, EEG abnormalities, and seizures. Rarely, deficiency or dependency causes seizures in infants. Seizures, particularly in infants, may be refractory to treatment with anticonvulsants. Normocytic, microcytic, or sideroblastic anemia can also develop.

Diagnosis

• Clinical evaluation

Vitamin B_6 deficiency should be considered in any infant who has seizures, any patient who has seizures refractory to treatment with anticonvulsants, and any patient with deficiencies of other B vitamins,

particularly in patients with alcoholism or protein-energy undernutrition. Diagnosis is usually clinical. There is no single accepted laboratory test of vitamin B_6 status; measurement of serum pyridoxal phosphate is most common.

Treatment

• Pyridoxine

• Elimination of risk factors when possible

For secondary deficiency, causes (eg, use of pyridoxine-inactivating drugs, malabsorption) should be corrected if possible. Usually, pyridoxine 50 to 100 mg po once/day corrects the deficiency in adults. Most people taking isoniazid should also be given pyridoxine 30 to 50 mg/day. For deficiency due to increased metabolic demand, amounts larger than the daily recommended intake may be required. For most cases of inborn errors of metabolism, high doses of pyridoxine may be effective.

Vitamin B_6 Toxicity

The ingestion of megadoses (> 500 mg/day) of pyridoxine (eg, taken to treat carpal tunnel syndrome or premenstrual syndrome although efficacy is unproved) may cause peripheral neuropathy with deficits in a stocking-glove distribution, including progressive sensory ataxia and severe impairment of position and vibration senses. Senses of touch, temperature, and pain are less affected. Motor and central nervous systems are usually intact.

Diagnosis is clinical. Treatment is to stop taking vitamin B_6. Recovery is slow and, for some patients, incomplete.

Vitamin B_{12}

Cobalamin is a general term for compounds with biologic vitamin B_{12} activity. These compounds are involved in nucleic acid metabolism, methyl transfer, and myelin synthesis and repair. They are necessary for the formation of normal RBCs.

Food-bound vitamin B_{12} is released in the stomach's acid environment and is bound to R protein (haptocorrin). Pancreatic enzymes cleave this B_{12} complex (B_{12}-R protein) in the small intestine. After cleavage, intrinsic factor, secreted by parietal cells in the gastric mucosa, binds with vitamin B_{12}. Intrinsic factor is required for absorption of vitamin B_{12}, which takes place in the terminal ileum.

Vitamin B_{12} in plasma is bound to transcobalamins I and II. Transcobalamin II is responsible for delivering vitamin B_{12} to tissues. The liver stores large amounts of vitamin B_{12}. Enterohepatic reabsorption helps retain vitamin B_{12}. Liver vitamin B_{12} stores can normally sustain physiologic needs for 3 to 5 yr if B_{12} intake stops (eg, in people who become vegans) and for months to 1 yr if enterohepatic reabsorption capacity is absent.

Large amounts of vitamin B_{12} seem to be nontoxic but are not recommended for regular use (ie, as a general tonic).

Vitamin B_{12} Deficiency

Dietary vitamin B_{12} deficiency usually results from inadequate absorption, but deficiency can develop in vegans who do not take vitamin supplements. Deficiency causes megaloblastic anemia, damage to the white matter of the spinal cord and brain, and peripheral neuropathy. Diagnosis is usually made by measuring serum vitamin B_{12} levels. The Schilling test helps determine etiology. Treatment consists of oral or parenteral vitamin B_{12}. Folate (folic acid) should not be used instead of vitamin B_{12} because folate may alleviate the anemia but allow

neurologic deficits to progress.

Etiology

Inadequate vitamin B_{12} intake is possible in vegans but is otherwise unlikely. Breastfed babies of vegan mothers may develop vitamin B_{12} deficiency by age 4 to 6 mo because their

[
Table 4-5. Causes of Vitamin B_{12} Deficiency]

liver stores (which are normally extensive) are limited and their rapid growth rate results in high demand.

Vitamin B_{12} deficiency usually results from inadequate absorption (see Table 4-5 and p. 153), which, in the elderly, most commonly results from decreased acid secretion. In such cases, crystalline vitamin B_{12} (such as that available in vitamin supplements) can be absorbed, but food-bound vitamin B_{12} is not liberated and absorbed normally. Inadequate absorption may occur in blind loop syndrome (with overgrowth of bacteria) or fish tapeworm infestation; in these cases, bacteria or parasites use ingested vitamin B_{12} so that less is available for absorption. Vitamin B_{12} absorption may be inadequate if ileal absorptive sites are destroyed by inflammatory bowel disease or are surgically removed. Less common causes of inadequate vitamin B_{12} absorption include chronic pancreatitis, gastric surgery, malabsorption syndromes, AIDS, use of certain drugs (eg, antacids, metformin), repeated exposure to nitrous oxide, and a genetic disorder causing malabsorption in the ileum (Imerslund-Graesbeck syndrome).

Pernicious anemia is often used synonymously with vitamin B_{12} deficiency. However, pernicious anemia specifically refers to anemia resulting from vitamin B_{12} deficiency caused by an autoimmune metaplastic atrophic gastritis with loss of intrinsic factor (see p. 133). Patients with classic pernicious anemia, most commonly younger adults, are at increased risk of stomach and other GI cancers.

Subacute combined degeneration refers to degenerative changes in the nervous system due to vitamin B_{12} deficiency; they affect mostly brain and spinal cord white matter. Demyelinating or axonal peripheral neuropathies can occur.

Symptoms and Signs

Anemia usually develops insidiously. It is often more severe than its symptoms indicate because its slow evolution allows physiologic adaptation. Occasionally, splenomegaly and hepatomegaly occur. Various GI symptoms, including weight loss and poorly localized abdominal pain, may occur. Glossitis, usually described as burning of the tongue, is uncommon.

Neurologic symptoms develop independently from and often without hematologic abnormalities. In early stages, decreased position and vibratory sensation in the extremities is accompanied by mild to moderate weakness and hyporeflexia. In later stages, spasticity, extensor plantar responses, greater loss of position and vibratory sensation in the lower extremities, and ataxia emerge. These deficits may develop in a stocking-glove distribution. Tactile, pain, and temperature sensations are usually spared but may be difficult to assess in the elderly.

Some patients are also irritable and mildly depressed. Paranoia (megaloblastic madness), delirium, confusion, spastic ataxia, and, at times, postural hypotension may occur in advanced cases. The confusion may be difficult to differentiate from age-related dementias, such as Alzheimer's disease.

Diagnosis

• CBC and vitamin B_{12} and folate levels

• Sometimes methylmalonic acid levels or Schilling test

Diagnosis is based on CBC and vitamin B_{12} and folate levels. It is important to remember that severe neurologic disease may occur without anemia or macrocytosis.

CBC detects megaloblastic anemia. Tissue deficiency and macrocytic indexes may precede the development of anemia. A vitamin B_{12} level < 200 pg/mL (< 145 pmol/L) indicates vitamin B_{12} deficiency. The folate level is measured because vitamin B_{12} deficiency must be differentiated from folate deficiency as a cause of megaloblastic anemia; folate supplementation can mask vitamin B_{12} deficiency and may alleviate megaloblastic anemia but allow the neurologic deficits to progress or even accelerate.

When clinical judgment suggests vitamin B_{12} deficiency but the vitamin B_{12} level is low-normal (200 to 350 pg/mL [145 to 260 pmol/L]) or hematologic indexes are normal, other tests can be done. Measuring serum methylmalonic acid (MMA) levels may be useful. An elevated MMA level supports vitamin B_{12} deficiency but may be due to renal failure. MMA levels can also be used to monitor the response to treatment. MMA levels remain normal in folate deficiency; homocysteine levels may be elevated with either vitamin B_{12} or folate deficiency. Less commonly, holotranscobalamin II (transcobalamin II-B_{12} complex) content is measured; when holotranscobalamin II is < 40 pg/mL (< 30 pmol/L), vitamin B_{12} is deficient.

After deficiency is diagnosed, additional tests may be indicated for younger adults but usually not for the elderly. Unless dietary vitamin B_{12} is obviously inadequate, measurement of serum gastrin levels or autoantibodies to intrinsic factor may be done; sensitivity and specificity of these tests may be poor.

Schilling test: The Schilling test is useful only if diagnosing intrinsic factor deficiency is important, as in classic pernicious anemia. This test is not necessary for most elderly patients. The Schilling test measures absorption of free radiolabeled vitamin B_{12}. Radiolabeled vitamin B_{12} is given orally, followed in 1 to 6 h by 1000 µg (1 mg) of parenteral vitamin B_{12}, which reduces uptake of radiolabeled vitamin B_{12} by the liver. Absorbed radiolabeled vitamin B_{12} is excreted in urine, which is collected for 24 h. The amount excreted is measured, and the percentage of total radiolabeled vitamin B_{12} is determined. If absorption is normal, ≥ 9% of the dose given appears in the urine. Reduced urinary excretion (< 5% if kidney function is normal) indicates inadequate vitamin B_{12} absorption. Improved absorption with the subsequent addition of intrinsic factor to radiolabeled vitamin B_{12} confirms the diagnosis of pernicious anemia. The test is often difficult to do or interpret because of incomplete urine collection or renal insufficiency. In addition, because the Schilling test does not measure absorption of protein-bound vitamin B_{12}, the test does not detect defective liberation of vitamin B_{12} from foods, which is common among the elderly. The Schilling test repletes vitamin B_{12} and can mask deficiency, so it should be done only after all other diagnostic tests and therapeutic trials.

If malabsorption is identified, the Schilling test can be repeated after a 2-wk trial of an oral antibiotic. If antibiotic therapy corrects malabsorption, the likely cause is intestinal overgrowth of bacteria (eg, blind-loop syndrome).

Treatment

• Supplemental vitamin B_{12}

Vitamin B_{12} 1000 to 2000 µg po can be given once/day to patients who do not have severe deficiency or neurologic symptoms or signs. A nasal gel preparation of vitamin B_{12} is available at a higher price. Large oral doses can be absorbed by mass action, even when intrinsic factor is absent. If the MMA level (sometimes used to monitor treatment) does not decrease, patients may not be taking vitamin B_{12}. For more severe deficiency, vitamin B_{12} 1 mg IM is usually given 1 to 4 times/wk for several weeks until hematologic abnormalities are corrected; then it is given once/mo.

Although hematologic abnormalities are usually corrected within 6 wk (reticulocyte count should improve within 1 wk), resolution of neurologic symptoms may take much longer. Neurologic symptoms that persist

for months or years become irreversible. In most elderly people with vitamin B_{12} deficiency and dementia, cognition does not improve after treatment. Vitamin B_{12} treatment must be continued for life unless the pathophysiologic mechanism for the deficiency is corrected.

Infants of vegan mothers should receive supplemental vitamin B_{12} from birth.

Vitamin C

Vitamin C (ascorbic acid) plays a role in collagen, carnitine, hormone, and amino acid formation. It is essential for wound healing and facilitates recovery from burns. Vitamin C is also an antioxidant, supports immune function, and facilitates the absorption of iron.

Vitamin C Deficiency

In developed countries, vitamin C deficiency can occur as part of general undernutrition, but severe deficiency (causing scurvy) is uncommon. Symptoms include fatigue, depression, and connective tissue defects (eg, gingivitis, petechiae, rash, internal bleeding, impaired wound healing). In infants and children, bone growth may be impaired. Diagnosis is usually clinical. Treatment consists of oral vitamin C.

Severe deficiency results in scurvy, a disorder characterized by hemorrhagic manifestations and abnormal osteoid and dentin formation.

Etiology

In adults, primary deficiency is usually due to inadequate diet. The need for dietary vitamin C is increased by febrile illnesses, inflammatory disorders (particularly diarrheal disorders), achlorhydria, smoking, thyrotoxicosis, iron deficiency, cold or heat stress, surgery, burns, and protein deficiency. Heat (eg, sterilization of formulas, cooking) can destroy some of the vitamin C in food.

Pathophysiology

Formation of intercellular cement substances in connective tissues, bones, and dentin is defective, resulting in weakened capillaries with subsequent hemorrhage and defects in bone and related structures.

Bone tissue formation becomes impaired, which, in children, causes bone lesions and poor bone growth. Fibrous tissue forms between the diaphysis and the epiphysis, and costochondral junctions enlarge. Densely calcified fragments of cartilage are embedded in the fibrous tissue. Subperiosteal hemorrhages, sometimes due to small fractures, may occur in children or adults.

Symptoms and Signs

In adults, symptoms develop after weeks to months of vitamin C depletion. Lassitude, weakness, irritability, weight loss, and vague myalgias and arthralgias may develop early.

Later, symptoms related to defects in connective tissues develop. Follicular hyperkeratosis, coiled hair, and perifollicular hemorrhages may develop. Gums may become swollen, purple, spongy, and friable; they bleed easily in severe deficiency. Eventually, teeth become loose and avulsed. Secondary infections may develop. Wounds heal poorly and tear easily, and spontaneous hemorrhages may occur, especially as ecchymoses in the skin of the lower limbs or as bulbar conjunctival hemorrhage.

Other symptoms and signs include femoral neuropathy due to hemorrhage into femoral sheaths (which may mimic deep venous thrombosis), lower-extremity edema, and painful bleeding or effusions within joints.

Diagnosis

• Usually, skin or gingival findings and risk factors

Diagnosis is usually made clinically in a patient who has skin or gingival signs and is at risk of vitamin C deficiency. Laboratory confirmation may be available. Anemia is common. Bleeding, coagulation, and PT are normal.

Skeletal x-rays can help diagnose childhood (but not adult) scurvy. Changes are most evident at the ends of long bones, particularly at the knee. Early changes resemble atrophy. Loss of trabeculae results in a ground-glass appearance. The cortex thins. A line of calcified, irregular cartilage (white line of Fraenkel) may be visible at the metaphysis. A zone of rarefaction or a linear fracture proximal and parallel to the white line may be visible as only a triangular defect at the bone's lateral margin but is specific. The epiphysis may be compressed. Healing subperiosteal hemorrhages may elevate and calcify the periosteum.

Laboratory diagnosis, which requires measuring blood ascorbic acid, is sometimes done at academic centers. Levels of < 0.6 mg/dL (< 34 µmol/L) are considered marginal; levels of < 0.2 mg/dL (< 11 µmol/L) indicate vitamin C deficiency. Measurement of ascorbic acid levels in the WBC-platelet layer of centrifuged blood is not widely available or standardized.

In adults, scurvy must be differentiated from arthritis, hemorrhagic disorders, gingivitis, and protein-energy undernutrition. Hyperkeratotic hair follicles with surrounding hyperemia or hemorrhage are almost pathognomonic. Bleeding gums, conjunctival hemorrhages, most petechiae, and ecchymoses are nonspecific.

Treatment

• Nutritious diet with supplemental ascorbic acid

For scurvy in adults, ascorbic acid 100 to 500 mg po tid is given for 1 to 2 wk, until signs disappear, and followed by a nutritious diet supplying 1 to 2 times the daily recommended intake. In scurvy, therapeutic doses of ascorbic acid restore the functions of vitamin C in a few days. The symptoms and signs usually disappear over 1 to 2 wk. Chronic gingivitis with extensive subcutaneous hemorrhage persists longer.

Prevention

Vitamin C 75 mg po once/day for women and 90 mg po once/day for men prevents deficiency. Smokers should consume an additional 35 mg/day. Five servings of most fruits and vegetables (recommended daily) provide > 200 mg of vitamin C.

Vitamin C Toxicity

The upper limit for vitamin C intake is 2000 mg/day. Up to 10 g/day of vitamin C are sometimes taken for unproven health benefits, such as preventing or shortening the duration of viral infections or slowing or reversing the progression of cancer or atherosclerosis. Such doses may acidify the urine, cause nausea and diarrhea, interfere with the healthy antioxidant-prooxidant balance in the body, and, in patients with thalassemia or hemochromatosis, promote iron overload. Intake below the upper limit does not have toxic effects in healthy adults.

Vitamin D

Vitamin D has 2 main forms: D_2 (ergocalciferol) and D_3 (cholecalciferol); the latter is the naturally occurring form and the form used for low-dose supplementation. Vitamin D_3 is synthesized in skin by exposure to direct sunlight (ultraviolet B radiation) and obtained in the diet chiefly in fish liver oils and salt water fish. In some developed countries, milk and other foods are fortified with vitamin D. Human breast milk is low in vitamin D, containing an average of only 10% of the amount in fortified cow's milk. Requirements for vitamin D increase with age because skin synthesis declines. Sunscreen use and dark skin pigmentation also reduce skin synthesis of vitamin D.

Vitamin D is a prohormone with several active metabolites that act as hormones. Vitamin D is metabolized by the liver to 25(OH)D, which is then converted by the kidneys to $1,25(OH)_2D$ (1,25-dihydroxycholecalciferol, calcitriol, or active vitamin D hormone). 25(OH)D, the major circulating form, has some metabolic activity, but $1,25(OH)_2D$ is the most metabolically active. The conversion to $1,25(OH)_2D$ is regulated by its own concentration, parathyroid hormone (PTH), and serum concentrations of Ca and phosphate.

[
Table 4-6. Actions of Vitamin D and its Metabolites]

Vitamin D affects many organ systems (see Table 4-6), but mainly it increases Ca and phosphate absorption from the intestine and promotes normal bone formation and mineralization. Vitamin D and related analogs may be used to treat psoriasis, hypoparathyroidism, renal osteodystrophy, and possibly leukemia and breast, prostate, and colon cancers; they may also be used for immunosuppression.

Vitamin D Deficiency and Dependency

Inadequate exposure to sunlight predisposes to vitamin D deficiency. Deficiency impairs bone mineralization, causing rickets in children and osteomalacia in adults and possibly contributing to osteoporosis. Treatment usually consists of oral vitamin D; Ca and phosphate are supplemented as needed. Prevention is often possible. Rarely, hereditary disorders cause impaired metabolism of vitamin D (dependency).

Vitamin D deficiency is a common cause of rickets and osteomalacia, but these disorders may also result from other conditions, such as various renal tubular disorders, familial hypophosphatemic (vitamin D-resistant) rickets (see p. 2991), chronic metabolic acidosis, hypoparathyroidism (which reduces vitamin D absorption), inadequate dietary Ca, and disorders or drugs that impair the mineralization of bone matrix.

Vitamin D deficiency causes hypocalcemia, which stimulates production of PTH, causing hyperparathyroidism. Hyperparathyroidism increases absorption, bone mobilization, and renal conservation of Ca but increases excretion of phosphate. As a result, the serum level of Ca may be normal, but because of hypophosphatemia, bone mineralization is impaired.

Etiology

Vitamin D deficiency may result from the following.

Inadequate exposure or intake: Inadequate direct sunlight exposure (or sunscreen use) and inadequate intake usually occur simultaneously to result in clinical deficiency. Susceptible people include the elderly (who are often undernourished and are not exposed to enough sunlight), and certain communities (eg, women and children who are confined to the home or who wear clothing that covers the entire body and face). Inadequate vitamin D stores are common among the elderly, particularly those who are house-bound, institutionalized, or hospitalized or who have had a hip fracture. Recommended direct sunlight exposure is 5 to 15 min (suberythemal dose) to arms and legs, or face, arms and hands, at least 3 times a week.

Reduced absorption: Malabsorption can deprive the body of dietary vitamin D; only a small amount of 25(OH)D is recirculated enterohepatically.

Abnormal metabolism: Vitamin D deficiency may result from defects in the production of 25(OH)D or $1,25(OH)_2D$. People with a chronic renal disorder commonly develop rickets or osteomalacia because renal production of $1,25\ (OH)_2D$ is decreased and phosphate levels are elevated. Hepatic dysfunction can also interfere with production of active vitamin D metabolites.

Type I hereditary vitamin D-dependent rickets is an autosomal recessive disorder characterized by absent or defective conversion of 25(OH)D to $1,25(OH)_2D$ in the kidneys. X-linked familial hypophosphatemia

reduces vitamin D synthesis in the kidneys. Many anticonvulsants and glucocorticoid use increase the need for vitamin D supplementation.

Resistance to effects of vitamin D: Type II hereditary vitamin D-dependent rickets has several forms and is due to mutations in the $1,25(OH)_2D$ receptor. This receptor affects the metabolism of gut, kidney, bone, and other cells. In this disorder, $1,25(OH)_2D$ is abundant but ineffective because the receptor is not functional.

Symptoms and Signs

Vitamin D deficiency can cause muscle aches, muscle weakness, and bone pain at any age.

Vitamin D deficiency in a pregnant woman causes deficiency in the fetus. Occasionally, deficiency severe enough to cause maternal osteomalacia results in rickets with metaphyseal lesions in neonates. In young infants, rickets causes softening of the entire skull (craniotabes). When palpated, the occiput and posterior parietal bones feel like a ping pong ball. In older infants with rickets, sitting and crawling are delayed, as is fontanelle closure; there is bossing of the skull and costochondral thickening. Costochondral thickening can look like beadlike prominences along the lateral chest wall (rachitic rosary). In children 1 to 4 yr, epiphyseal cartilage at the lower ends of the radius, ulna, tibia, and fibula enlarges; kyphoscoliosis develops, and walking is delayed. In older children and adolescents, walking is painful; in extreme cases, deformities such as bowlegs and knock-knees develop.

Tetany is caused by hypocalcemia and may accompany infantile or adult vitamin D deficiency. Tetany may cause paresthesias of the lips, tongue, and fingers; carpopedal and facial spasm; and, if very severe, seizures. Maternal deficiency can cause tetany in neonates.

Osteomalacia predisposes to fractures. In the elderly, hip fractures may result from only minimal trauma.

Diagnosis

• Levels of 25(OH)D (D_2+D_3)

Diagnosis may be suspected based on any of the following:

• A history of inadequate sunlight exposure or dietary intake

• Symptoms and signs of rickets, osteomalacia, or neonatal tetany

• Characteristic bone changes seen on x-ray

X-rays of the radius and ulna plus serum levels of Ca, phosphate, alkaline phosphatase, PTH, and 25(OH)D are needed to differentiate vitamin D deficiency from other causes of bone demineralization.

Assessment of vitamin D status and serologic tests for syphilis can be considered for infants with craniotabes based on the history and physical, but most cases of craniotabes resolve spontaneously. Rickets can be distinguished from chondrodystrophy because the latter is characterized by a large head, short extremities, thick bones, and normal serum Ca, phosphate, and alkaline phosphatase levels.

Tetany due to infantile rickets may be clinically indistinguishable from seizures due to other causes. Blood tests and clinical history may help distinguish them.

Bone changes, seen on x-rays, precede clinical signs. In rickets, changes are most evident at the lower ends of the radius and ulna. The diaphyseal ends lose their sharp, clear outline; they are cup-shaped and show a spotty or fringy rarefaction. Later, because the ends of the radius and ulna have become noncalcified and radiolucent, the distance between them and the metacarpal bones appears increased. The bone matrix elsewhere also becomes more radiolucent. Characteristic deformities result from the bones bending at the cartilage-shaft junction because the shaft is weak. As healing begins, a thin white

line of calcification appears at the epiphysis, becoming denser and thicker as calcification proceeds. Later, the bone matrix becomes calcified and opacified at the subperiosteal level.

In adults, bone demineralization, particularly in the spine, pelvis, and lower extremities, can be seen on x-rays; the fibrous lamellae can also be seen, and incomplete ribbonlike areas of demineralization (pseudofractures, Looser's lines, Milkman's syndrome) appear in the cortex.

Because levels of serum 25(OH)D reflect body stores of vitamin D and correlate with symptoms and signs of vitamin D deficiency better than levels of other vitamin D metabolites, 25(OH)D (D_2+D_3) measurement is generally considered the best way to diagnose deficiency. Goal 25(OH)D levels are 30 to 40 ng/mL (about 75 to 100 nmol/L); whether higher levels may be beneficial remains uncertain.

If the diagnosis is unclear, serum levels of 1,25$(OH)_2$D and urinary Ca concentration can be measured. In severe deficiency, serum 1,25$(OH)_2$D is abnormally low, usually undetectable. Urinary Ca is low in all forms of the deficiency except those associated with acidosis.

In vitamin D deficiency, serum Ca may be low or, because of secondary hyperparathyroidism, may be normal. Serum phosphate usually decreases, and serum alkaline phosphatase usually increases. Serum PTH is elevated.

Type I hereditary vitamin D-dependent rickets results in normal serum 25(OH)D, low serum 1,25$(OH)_2$D and Ca, and normal or low serum phosphate.

Treatment

• Correction of Ca and phosphate deficiencies

• Supplemental vitamin D

Ca deficiency (which is common) and phosphate deficiency should be corrected. As long as Ca and phosphate intake is adequate, adults with osteomalacia and children with uncomplicated rickets can be cured by giving vitamin D 40 µg (1600 IU) po once/day. Serum 25(OH)D and 1,25$(OH)_2$D begin to increase within 1 or 2 days. Serum Ca and phosphate increase and serum alkaline phosphatase decreases within about 10 days. During the 3rd wk, enough Ca and phosphate are deposited in bones to be visible on x-rays. After about 1 mo, the dose can usually be reduced gradually to the usual maintenance level of 10 to 15 µg (400 to 600 IU) once/day. If tetany is present, vitamin D should be supplemented with IV Ca salts for up to 1 wk (see p. 841). Elderly patients may need 25 to ≥ 50 µg (1000 to ≥ 2000 IU) daily to maintain a 25(OH)D level > 30 ng/mL (> 75 nmol/L); this dose is higher than the recommended daily allowance (RDA) for people > 70 yr (600 IU) and may exceed the current upper limit of 2000 IU/day.

Because rickets and osteomalacia due to defective production of vitamin D metabolites are vitamin D-resistant, they do not respond to the doses usually effective for rickets due to inadequate intake. Endocrinologic evaluation is required because treatment depends on the specific defect. When 25(OH)D production is defective, vitamin D 50 µg (2000 IU) once/day increases serum levels and results in clinical improvement. Patients with kidney disorders often need 1,25$(OH)_2$D supplementation.

Type I hereditary vitamin D-dependent rickets responds to 1,25$(OH)_2$D 1 to 2 µg po once/day. Some patients with type II hereditary vitamin D-dependent rickets respond to very high doses (eg, 10 to 24 µg/day) of 1,25$(OH)_2$D; others require long-term infusions of Ca.

Prevention

Dietary counseling is particularly important in communities whose members are at risk of vitamin D deficiency. Fortifying unleavened chapati flour with vitamin D (125 µg/kg) has been effective among Indian immigrants in Britain. The benefits of sunlight exposure for vitamin D status must be weighed against the increased skin damage and skin cancer risks.

All breastfed infants should be given supplemental vitamin D 5 µg (200 IU) once/day from birth to 6 mo; at 6 mo, a more diversified diet is available. For adolescents at risk, a single IM dose of ergocalciferol 2.5 mg (100,000 IU) given in the fall can maintain adequate 25(OH)D levels throughout the winter. The recommended daily allowance (RDA) for vitamin D is 400 IU for people aged 51 to 70 and 600 IU for those >70; many consider this intake too low, and the 2005 Dietary Guidelines for Americans recommends that healthy older adults consume 1000 IU/day.

Vitamin D Toxicity

Usually, vitamin D toxicity results from taking excessive amounts. Marked hypercalcemia commonly causes symptoms. Diagnosis is typically based on elevated blood levels of 25(OH)D. Treatment consists of stopping vitamin D, restricting dietary Ca, restoring intravascular volume deficits, and, if toxicity is severe, giving corticosteroids or bisphosphonates.

Because synthesis of $1,25(OH)_2D$ (the most active metabolite of vitamin D) is tightly regulated, vitamin D toxicity usually occurs only if excessive doses (prescription or megavitamin) are taken. Vitamin D 1000 µg (40,000 IU)/day causes toxicity within 1 to 4 mo in infants. In adults, taking 1250 µg (50,000 IU)/day for several months can cause toxicity. Vitamin D toxicity can occur iatrogenically when hypoparathyroidism is treated too aggressively (see p. 844).

Symptoms and Signs

The main symptoms result from hypercalcemia. Anorexia, nausea, and vomiting can develop, often followed by polyuria, polydipsia, weakness, nervousness, pruritus, and eventually renal failure. Proteinuria, urinary casts, azotemia, and metastatic calcifications (particularly in the kidneys) can develop.

Diagnosis

• Hypercalcemia plus risk factors or elevated serum 25(OH)D levels

A history of excessive vitamin D intake may be the only clue differentiating vitamin D toxicity from other causes of hypercalcemia. Elevated serum Ca levels of 12 to 16 mg/dL (3 to 4 mmol/L) are a constant finding when toxic symptoms occur. Serum 25(OH)D levels are usually elevated > 150 ng/mL (> 375 nmol/L). Levels of $1,25(OH)_2D$, which need not be measured to confirm the diagnosis, may be normal.

Serum Ca should be measured often (weekly at first, then monthly) in all patients receiving large doses of vitamin D, particularly the potent $1,25(OH)_2D$.

Treatment

• IV hydration plus corticosteroids or bisphosphonates

After stopping vitamin D intake, hydration with IV normal saline and corticosteroids or bisphosphonates (which inhibit bone resorption) are used to reduce blood Ca levels.

Kidney damage or metastatic calcifications, if present, may be irreversible.

Vitamin E

Vitamin E is a group of compounds (including tocopherols and tocotrienols) that have similar biologic activities. The most biologically active is α-tocopherol, but β-, γ-, and δ-tocopherols, 4 tocotrienols, and several stereoisomers may also have important biologic activity. These compounds act as antioxidants, which prevent lipid peroxidation of polyunsaturated fatty acids in cellular membranes. Plasma tocopherol levels vary with total plasma lipid levels. Normally, the plasma α-tocopherol level is 5 to 20 µg/mL (11.6 to 46.4 µmol/L). High-dose vitamin E supplements do not protect against cardiovascular disorders;whether

supplements can protect against Alzheimer's disease, tardive dyskinesia, and prostate cancer among smokers is controversial.

Although the amount of vitamin E in many fortified foods and supplements is given in IU, current recommendations are to use mg.

Vitamin E Deficiency

Dietary vitamin E deficiency is common in developing countries; deficiency among adults in developed countries is uncommon and usually due to fat malabsorption. The main symptoms are hemolytic anemia and neurologic deficits. Diagnosis is based on measuring the ratio of plasma α-tocopherol to total plasma lipids; a low ratio suggests vitamin E deficiency. Treatment consists of oral vitamin E, given in high doses if there are neurologic deficits or if deficiency results from malabsorption.

Vitamin E deficiency causes fragility of RBCs and degeneration of neurons, particularly peripheral axons and posterior column neurons.

Etiology

In developing countries, the most common cause is inadequate intake of vitamin E. In developed countries, the most common causes are disorders that cause fat malabsorption, including abetalipoproteinemia (Bassen-Kornzweig syndrome, due to genetic absence of apolipoprotein B), chronic cholestatic hepatobiliary disease, pancreatitis, short bowel syndrome, and cystic fibrosis. A rare genetic form of vitamin E deficiency without fat malabsorption results from defective liver metabolism.

Symptoms and Signs

The main symptoms are mild hemolytic anemia and nonspecific neurologic deficits. Abetalipoproteinemia results in progressive neuropathy and retinopathy in the first 2 decades of life (see p. 904).

Vitamin E deficiency may contribute to retinopathy of prematurity (also called retrolental fibroplasia) in premature infants and to some cases of intraventricular and subependymal hemorrhage in neonates. Affected premature neonates have muscle weakness.

In children, chronic cholestatic hepatobiliary disease or cystic fibrosis causes neurologic deficits, including spinocerebellar ataxia with loss of deep tendon reflexes, truncal and limb ataxia, loss of vibration and position senses, ophthalmoplegia, muscle weakness, ptosis, and dysarthria.

In adults with malabsorption, vitamin E deficiency very rarely causes spinocerebellar ataxia because adults have large vitamin E stores in adipose tissue.

Diagnosis

• Low α-tocopherol level or low ratio of serum α-tocopherol to serum lipids

Without a history of inadequate intake or a predisposing condition, vitamin E deficiency is unlikely. Confirmation usually requires measuring the vitamin level. Measuring RBC hemolysis in response to peroxide can suggest the diagnosis but is nonspecific. Hemolysis increases as vitamin E deficiency impairs RBC stability.

Measuring the serum α-tocopherol level is the most direct method of diagnosis. In adults, vitamin E deficiency is suggested if the α-tocopherol level is < 5 μg/mL (< 11.6 μmol/L). Because abnormal lipid levels can affect vitamin E status, a low ratio of serum α-tocopherol to lipids (< 0.8 mg/g total lipid) is the most accurate indicator in adults with hyperlipidemia.

In children and adults with abetalipoproteinemia, serum α-tocopherol levels are usually undetectable.

Treatment

• Supplemental α-tocopherol

If malabsorption causes clinically evident deficiency, α-tocopherol 15 to 25 mg/kg po once/day should be given. However, larger doses given by injection are required to treat neuropathy during its early stages or to overcome the defect of absorption and transport in abetalipoproteinemia.

Prevention

Although premature neonates may require supplementation, human milk and commercial formulas have enough vitamin E for full-term neonates.

Vitamin E Toxicity

Many adults take relatively large amounts of vitamin E (α-tocopherol 400 to 800 mg/day) for months to years without any apparent harm. Occasionally, muscle weakness, fatigue, nausea, and diarrhea occur. The most significant risk is bleeding. However, bleeding is uncommon unless the dose is > 1000 mg/day or the patient takes oral coumarin or warfarin. Thus, the upper limit for adults aged ≥19 yr is 1000 mg for any form of α-tocopherol. Recent analyses of previous studies report that high vitamin E intakes may increase the risk of hemorrhagic stroke and premature death.

Vitamin K

Vitamin K_1 (phylloquinone) is dietary vitamin K. Dietary fat enhances its absorption. Infant formulas contain supplemental vitamin K. Vitamin K_2 refers to a group of compounds (menaquinones) synthesized by bacteria in the intestinal tract; the amount synthesized does not satisfy the vitamin K requirement.

Vitamin K controls the formation of coagulation factors II (prothrombin), VII, IX, and X in the liver. Other coagulation factors dependent on vitamin K are protein C, protein S, and protein Z; proteins C and S are anticoagulants. Metabolic pathways conserve vitamin K. Once vitamin K has participated in formation of coagulation factors, the reaction product, vitamin K epoxide, is enzymatically converted to the active form, vitamin K hydroquinone.

The actions of vitamin K-dependent proteins require Ca. The vitamin K-dependent proteins, osteocalcin and matrix γ-carboxy-glutamyl (Gla) protein, may have important roles in bone and other tissues. Forms of vitamin K are common therapy for osteoporosis in Japan and other countries.

Vitamin K Deficiency

Vitamin K deficiency results from extremely inadequate intake, fat malabsorption, or use of coumarin anticoagulants. Deficiency is particularly common among breastfed infants. It impairs clotting. Diagnosis is suspected based on routine coagulation study findings and confirmed by response to vitamin K. Treatment consists of vitamin K given orally or, when fat malabsorption is the cause or risk of bleeding is high, parenterally.

Vitamin K deficiency decreases levels of prothrombin and other vitamin K-dependent coagulation factors, causing defective coagulation and, potentially, bleeding.

Etiology

Worldwide, vitamin K deficiency causes infant morbidity and mortality. Vitamin K deficiency causes hemorrhagic disease of the newborn, which usually occurs 1 to 7 days postpartum. In affected neonates, birth trauma can cause intracranial hemorrhage. Neonates are prone to vitamin K deficiency because of the following:

• The placenta transmits lipids and vitamin K relatively poorly.

• The neonatal liver is immature with respect to prothrombin synthesis.

• Breast milk is low in vitamin K, containing about 2.5 µg/L (cow's milk contains 5000 µg/L).

• The neonatal gut is sterile during the first few days of life.

Late hemorrhagic disease (occurring 3 to 8 wk postpartum) is usually associated with breastfeeding, malabsorption, or a liver disorder. If the mother has taken phenytoin anticonvulsants, coumarin anticoagulants, or cephalosporin antibiotics, the risk of both types of hemorrhagic disease is increased.

In healthy adults, dietary vitamin K deficiency is uncommon because vitamin K is widely distributed in green vegetables and the bacteria of the normal gut synthesize menaquinones. However, biliary obstruction, malabsorption, cystic fibrosis, and resection of the small intestine can contribute to vitamin K deficiency.

Coumarin anticoagulants interfere with the synthesis of vitamin K-dependent coagulation proteins (factors II, VII, IX, and X) in the liver. Certain antibiotics (particularly some cephalosporins and other broad-spectrum antibiotics), salicylates, megadoses of vitamin E, and hepatic insufficiency increase risk of bleeding in patients with vitamin K deficiency.

Symptoms and Signs

Bleeding is the usual manifestation. Easy bruisability and mucosal bleeding (especially epistaxis, GI hemorrhage, menorrhagia, and hematuria) can occur. Blood may ooze from puncture sites or incisions.

Hemorrhagic disease of the newborn and late hemorrhagic disease in infants may cause cutaneous, GI, intrathoracic, or, in the worst cases, intracranial bleeding. If obstructive jaundice develops, bleeding—if it occurs—usually begins after the 4th or 5th day. It may begin as a slow ooze from a surgical incision, the gums, the nose, or GI mucosa, or it may begin as massive bleeding into the GI tract.

Diagnosis

• Usually, prolonged PT that decreases after phytonadione

Vitamin K deficiency or antagonism (due to coumarin anticoagulants) is suspected when abnormal bleeding occurs in a patient at risk. Blood coagulation studies can preliminarily confirm the diagnosis. PT, usually reported as the INR, is prolonged, but PTT, thrombin time, platelet count, bleeding time, and levels of fibrinogen, fibrin-split products, and D-dimer are normal. If phytonadione (USP generic name for vitamin K_1) 1 mg IV significantly decreases PT within 2 to 6 h, a liver disorder is not the likely cause, and the diagnosis of vitamin K deficiency is confirmed. Some centers can detect vitamin K deficiency more directly by measuring the serum vitamin level. The serum level of vitamin K_1 ranges from 0.2 to 1.0 ng/mL in healthy people consuming adequate quantities of vitamin K_1 (50 to 150 µg/day). Knowing vitamin K intake can help interpret serum levels; recent intake affects levels in serum but not in tissues.

More sensitive indicators of vitamin K status, such as PIVKA (*P*rotein *I*nduced in *V*itamin *K A*bsence or *A*ntagonism) and under-carboxylated osteocalcin, are under study.

Treatment

• Phytonadione

Whenever possible, phytonadione should be given po or sc. The usual adult dose is 5 to 20 mg. (Rarely, even when phytonadione is correctly diluted and given slowly, IV replacement can result in anaphylaxis or anaphylactoid reactions.) INR usually decreases within 6 to 12 h. The dose may be repeated in 6 to 8 h if INR has not decreased satisfactorily. Phytonadione 2.5 to 10 mg po is indicated for nonemergency correction of a prolonged INR in patients taking anticoagulants. Correction usually occurs within 6 to 8 h. When only partial correction of INR is desirable (eg, when INR should remain slightly elevated because of

a prosthetic heart valve), lower doses (eg, 1 to 2.5 mg) of phytonadione can be given.

In infants, bleeding due to deficiency can be corrected by giving phytonadione 1 mg sc or IM once. The dose is repeated if INR remains elevated. Higher doses may be necessary if the mother has been taking oral anticoagulants.

Prevention

Phytonadione 0.5 to 1 mg IM (or 0.3 mg/kg for preterm infants) is recommended for all neonates within 6 h of birth to reduce the incidence of intracranial hemorrhage due to birth trauma and of classic hemorrhagic disease of the newborn (increased bleeding risks 1 to 7 days after birth). It is also used prophylactically before surgery. Some clinicians recommend that pregnant women taking anticonvulsants receive phytonadione 10 mg po once/day for the 1 mo or 20 mg po once/day for the 2 wk before delivery. The low vitamin K_1 content in breast milk can be increased by increasing maternal dietary intake of phylloquinone to 5 mg/day.

Vitamin K Toxicity

Vitamin K_1 (phylloquinone) is not toxic when consumed orally, even in large amounts. However, menadione (a synthetic, water-soluble vitamin K precursor) can cause toxicity and should not be used to treat vitamin K deficiency.

Chapter 5. Mineral Deficiency and Toxicity

Introduction

Six macrominerals are required by people in gram amounts. Four (Na, K, Ca, and Mg) are cations; two (Cl and P) are accompanying anions (see p. 820). Daily requirements range from 0.3 to 2.0 g. Bone, muscle, heart, and brain function depend on these minerals.

Nine trace minerals (microminerals) are required by people in minute amounts: chromium, copper, iodine, iron, fluorine, manganese, molybdenum, selenium, and zinc. (For sources, functions, effects of deficiency and toxicity, and dietary requirements, see Tables 5-1 and 5-2.) All trace minerals are toxic at high levels; some minerals (arsenic, nickel, and chromium) may be carcinogens.

Mineral deficiencies (except of iodine, iron, and zinc) do not often develop spontaneously in adults on ordinary diets; infants are more vulnerable because their growth is rapid and intake varies. Trace mineral imbalances can result from hereditary disorders (eg, hemochromatosis, Wilson's disease), kidney dialysis, parenteral nutrition, or restrictive diets prescribed for people with inborn errors of metabolism.

Chromium

Only 1 to 3% of biologically active trivalent chromium (Cr) is absorbed. Normal plasma levels are 0.05 to 0.50 µg/L (1.0 to 9.6 nmol/L). Chromium potentiates insulin activity and increases the growth rate in undernourished children. Supplements do not enhance muscle size or strength in men.

Deficiency: Four patients receiving long-term TPN developed possible chromium deficiency, with glucose intolerance, weight loss, ataxia, and peripheral neuropathy. Symptoms resolved in 3 who were given trivalent chromium 150 to 250 mg.

Toxicity: High doses of trivalent chromium given parenterally cause skin irritation, but lower doses given orally are not toxic. Exposure to hexavalent chromium (CrO_3) in the workplace may irritate the skin, lungs, and GI tract and may cause perforation of the nasal septum and lung carcinoma.

Copper

Copper is a component of many body proteins; almost all of the body's copper is bound to copper proteins. Unbound (free) copper ions are toxic. Genetic mechanisms control the incorporation of copper into apoproteins and the processes that prevent toxic accumulation of copper in the body. Copper absorbed in excess of metabolic requirements is excreted through bile.

[**Table 5-1.** Trace Minerals]

Acquired Copper Deficiency

If the genetic mechanisms controlling copper metabolism are normal, dietary deficiency rarely causes clinically significant copper deficiency. The only reported causes are kwashiorkor, persistent infantile diarrhea (usually associated with a diet limited to milk), severe malabsorption (as in sprue), and excessive zinc intake.

Deficiency may cause neutropenia, impaired bone calcification, and hypochromic anemia not responsive to iron supplements.

Diagnosis is based on low serum levels of copper and ceruloplasmin, although these tests are not always reliable. Treatment is directed at the cause, and copper 1.5 to 3 mg/day po (usually as copper sulfate) is given.

Inherited Copper Deficiency

(Menkes Syndrome)

Inherited copper deficiency occurs in male infants who inherit a mutant X-linked gene. Incidence is about 1 in 50,000 live births. Copper is deficient in the liver, serum, and essential copper proteins, including cytochrome-c oxidase, ceruloplasmin, and lysyl oxidase.

Symptoms are severe intellectual disability, vomiting, diarrhea, protein-losing enteropathy, hypopigmentation, bone changes, and arterial rupture; the hair is sparse, steely, or kinky.

Diagnosis

• Serum copper and ceruloplasmin levels

• Serum levels of dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in infants at risk

Diagnosis is based on low copper and ceruloplasmin levels in serum, although these tests are not always reliable. Because early diagnosis and treatment seem to result in a better prognosis, the disorder is ideally detected before age 2 wk. However, diagnostic accuracy of these tests is limited. Thus, infants at risk (eg, those with a family history) can be screened by measuring dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in serum. A dihydroxyphenylacetic acid:dihydroxyphenylglycol ratio of > 4 seems to indicate deficiency, and a dopamine:norepinephrine ratio of > 0.2 seems to confirm it.

Treatment

• Copper histidine

Parenteral copper is usually given as copper histidine 250 µg sc bid to age 1 yr, then 250 µg sc once/day until age 3 yr; monitoring kidney function is essential during treatment. Despite early treatment, many children have abnormal neurodevelopment.

Acquired Copper Toxicity

Acquired copper toxicity can result from ingesting or absorbing excess copper (eg, from ingesting an acidic food or beverage that has had prolonged contact with a copper container). Self-limited gastroenteritis with nausea, vomiting, and diarrhea may occur.

[**Table 5-2.** Guidelines for Daily Intake of Minerals]

More severe toxicity results from ingestion (usually with suicidal intent) of gram quantities of a copper salt (eg, copper sulfate) or from absorption of large amounts through the skin (eg, if compresses saturated with a solution of a copper salt are applied to large areas of burned skin). Hemolytic anemia and anuria can result and may be fatal.

Indian childhood cirrhosis, non-Indian childhood cirrhosis, and idiopathic copper toxicity are probably identical disorders in which excess copper causes cirrhosis. All seem to be caused by ingesting milk that has been boiled or stored in corroded copper or brass vessels. Recent studies suggest that idiopathic copper toxicity may develop only in infants with an unknown genetic defect.

Diagnosis usually requires liver biopsy, which shows Mallory hyalin bodies.

Treatment

• Chelation

• Supportive measures

For copper toxicity due to ingesting grams of copper, prompt gastric lavage is done. Copper toxicity that causes complications such as hemolytic anemia, anuria, or hepatotoxicity is also treated with either oral penicillamine 250 mg q 6 h to 750 mg q 12 h (1000 to 1500 mg/day in 2 to 4 doses) or dimercaprol 3 to 5 mg/kg IM q 4 h for 2 days, then q 4 to 6 h (see also Table 340-4 and copper salts in Table 340-8). If used early, hemodialysis may be effective. Occasionally, copper toxicity is fatal despite treatment.

Inherited Copper Toxicity

(Wilson's Disease)

Inherited copper toxicity results in accumulation of copper in the liver and other organs. Hepatic or neurologic symptoms develop. Diagnosis is based on a low serum ceruloplasmin level, high urinary excretion of copper, and sometimes liver biopsy results. Treatment consists of a low-copper diet and chelation, usually with penicillamine or dimercaprol.

Wilson's disease is a progressive disorder of copper metabolism that affects 1 person in 30,000. Affected people are homozygous for the mutant recessive gene, located on chromosome 13. Heterozygous carriers, who constitute about 1.1% of the population, are asymptomatic.

Pathophysiology

The genetic defect impairs copper transport. The impaired transport decreases copper secretion into the bile, thus causing the copper overload and resultant accumulation in the liver, which begins at birth. The impaired transport also interferes with incorporation of copper into the copper protein ceruloplasmin, thus decreasing serum levels of ceruloplasmin.

Hepatic fibrosis develops, ultimately causing cirrhosis. Copper diffuses out of the liver into the blood, then into other tissues. It is most destructive to the brain but also damages the kidneys and reproductive organs and causes hemolytic anemia. Some copper is deposited in Descemet's membrane of the cornea, causing Kayser-Fleischer rings.

Symptoms and Signs

Symptoms usually develop between ages 5 and 40. In almost half of patients, particularly adolescents, the first symptom is hepatitis—acute, chronic active, or fulminant. But hepatitis may develop at any time. In about 40% of patients, particularly young adults, the first symptoms reflect CNS involvement. Motor deficits are common, including any combination of tremors, dystonia, dysarthria, dysphagia, chorea, drooling, and incoordination. Sometimes the first symptoms are cognitive or psychiatric abnormalities. In 5 to 10% of patients, the first symptom is incidentally noted gold or greenish gold Kayser-Fleischer rings or crescents (due to copper deposits in the cornea), amenorrhea or repeated miscarriages, or hematuria.

Diagnosis

• Slit-lamp examination for Kayser-Fleischer rings

• Serum ceruloplasmin and 24-h urinary copper excretion

• Sometimes confirmation by penicillamine provocation test or liver biopsy

Wilson's disease should be suspected in people < 40 with any of the following:

• An unexplained hepatic, neurologic, or psychiatric disorder

• An unexplained persistent elevation in hepatic transaminases

• A sibling, parent, or cousin with Wilson's disease

• Fulminant hepatitis

If Wilson's disease is suspected, slit-lamp examination for Kayser-Fleischer rings is required, and serum ceruloplasmin and copper levels and 24-h urinary copper excretion are measured. Transaminase levels are also often measured; high levels are consistent with the diagnosis.

Kayser-Fleischer rings: These rings plus typical motor neurologic abnormalities or a decrease in ceruloplasmin are nearly pathognomonic for Wilson's disease. Rarely, these rings occur in other liver disorders (eg, biliary atresia, primary biliary cirrhosis), but ceruloplasmin levels should be unaffected.

Ceruloplasmin: Serum ceruloplasmin (normally 20 to 35 mg/dL) is usually low in Wilson's disease but can be normal. It can also be low in heterozygous carriers and those with other liver disorders (eg, viral hepatitis, drug- or alcohol-induced liver disease). A low ceruloplasmin level in a patient with a Kayser-Fleischer ring is diagnostic. Also, a level of < 5 mg/dL is highly suggestive regardless of clinical findings.

Serum copper: Despite the copper accumulation in the body, serum copper levels are decreased because of the decreased ceruloplasmin levels.

Urinary copper excretion: In Wilson's disease, 24-h urinary copper excretion (normally, ≤ 30 µg/day) is usually > 100 µg/day. If serum ceruloplasmin is low and urinary copper excretion is high, diagnosis is clear. If levels are equivocal, measuring urinary copper excretion after penicillamine is given (penicillamine provocation test) may confirm the diagnosis; this test is not usually done in adults because cutoff values are not well-established.

Liver biopsy: In unclear cases (eg, elevated transaminases, no Kayser-Fleischer rings, indeterminate values for ceruloplasmin and urinary copper), the diagnosis is made by doing a liver biopsy to measure hepatic copper concentration. However, false-negative results may occur because of a sampling error (due to large variations in copper concentrations in the liver) or fulminant hepatitis (causing necrosis that releases large amounts of copper).

Screening: Because early treatment is most effective, screening is indicated for anyone who has a sibling, cousin, or parent with Wilson's disease. Screening consists of a slit-lamp examination and measurement of transaminase levels, serum copper and ceruloplasmin, and 24-h urine copper excretion. If any results are abnormal, liver biopsy is done to measure hepatic copper concentration. Infants should not be tested until after age 1 yr because ceruloplasmin levels are low during the first few months of life. Children < 6 yr with normal test results should be retested 5 to 10 yr later.

Genetic testing is under investigation.

Prognosis

Prognosis is usually good, unless disease is advanced before treatment begins. Untreated Wilson's disease is fatal, usually by age 30.

Treatment

• Penicillamine or another chelating drug if needed to remove accumulated copper

• Low-copper diet

• For maintenance, lifelong low-dose chelation therapy or oral zinc

Continual, lifelong treatment is mandatory regardless of whether symptoms are present. Accumulated copper should be removed with chelating drugs. A low-copper diet (eg, avoiding beef liver, cashews, black-eyed peas, vegetable juice, shellfish, mushrooms, and cocoa) and use of either low-dose chelation

therapy or oral zinc can prevent copper from accumulating.

Penicillamine is the most commonly used chelating drug but has considerable toxicity (eg, fever, rash, neutropenia, thrombocytopenia, proteinuria). Cross-reactivity may occur in people with penicillin allergy. Patients > 5 yr are given oral doses of 62.5 mg q 6 h to 250 mg q 12 h (250 to 500 mg/day in 2 to 4 doses) and slowly increased to a maximum of 250 mg q 6 h to 750 mg q 12 h (1000 to 1500 mg/day in 2 to 4 doses). Younger children are given 10 mg/kg bid or 6.7 mg/kg tid (20 mg/kg/d) po. Pyridoxine 25 mg po once/day is given with penicillamine. Occasionally, use of penicillamine is associated with worsening neurologic symptoms.

Trientine hydrochloride is an alternative treatment to penicillamine. Doses are 375 to 750 mg po bid or 250 to 500 mg po tid (750 to 1500 mg/day).

Zinc acetate 50 mg po tid can prevent reaccumulation of copper in patients who cannot tolerate penicillamine or trientine or who have neurologic symptoms that do not respond to the other drugs. (CAUTION: *Penicillamine or trientine must not be given with zinc because either drug can bind zinc, forming a compound with no therapeutic effect*.)

Poor long-term adherence to drug therapy is common. After 1 to 5 yr of therapy, lower dose maintenance drug therapy can be considered. Regular follow-up care with an expert in liver disease is recommended.

Liver transplantation may be lifesaving for patients who have Wilson's disease and fulminant hepatic failure or severe hepatic insufficiency refractory to drugs.

Fluorine

Most of the body's fluorine (F) is contained in bones and teeth. Fluoride (the ionic form of fluorine) is widely distributed in nature. The main source of fluoride is fluoridated drinking water.

Deficiency: Fluorine deficiency can lead to dental caries and possibly osteoporosis. Fluoridation of water that contains < 1 ppm (the ideal) reduces the incidence of dental caries. If a child's drinking water is not fluoridated, oral fluoride supplements can be prescribed.

Toxicity: Excess fluorine can accumulate in teeth and bones, causing fluorosis. Drinking water containing > 10 ppm is a common cause. Permanent teeth that develop during high fluoride intake are most likely to be affected. Exposure must be much greater to affect deciduous teeth.

The earliest signs are chalky white, irregularly distributed patches on the surface of the enamel; these patches become stained yellow or brown, producing a characteristic mottled appearance. Severe toxicity weakens the enamel, pitting its surface. Bony changes, including osteosclerosis, exostoses of the spine, and genu valgum, can develop but only in adults after prolonged high intake of fluoride.

No tests to diagnose toxicity are available.

Treatment involves reducing fluoride intake; eg, in areas with high fluoride water levels, patients should not drink fluoridated water or take fluoride supplements. Children should always be told not to swallow fluoridated toothpastes.

Iodine

In the body, iodine (I) is involved primarily in the synthesis of 2 thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). Iodine occurs in the environment and in the diet primarily as iodide. In adults, about 80% of the iodide absorbed is trapped by the thyroid gland. Most environmental iodine occurs in seawater as iodide; a small amount enters the atmosphere and, through rain, enters ground water and soil near the sea. Thus, people living far from the sea and at higher altitudes are at particular risk of deficiency. Fortifying table salt with iodide (typically 70 µg/g) helps ensure adequate intake (150 µg/day). Requirements are higher for pregnant (220 µg/day) and breastfeeding (290 µg/day) women.

Iodine Deficiency

Deficiency is rare in areas where iodized salt is used but common worldwide. Iodine deficiency develops when iodide intake is < 20 µg/day. In mild or moderate deficiency, the thyroid gland, influenced by thyroid-stimulating hormone (TSH), hypertrophies to concentrate iodide in itself, resulting in colloid goiter. Usually, patients remain euthyroid; however, severe iodine deficiency in adults may cause hypothyroidism (endemic myxedema). It can decrease fertility and increase risk of stillbirth, spontaneous abortion, and prenatal and infant mortality. Severe maternal iodine deficiency retards fetal growth and brain development, sometimes resulting in birth defects, and, in infants, causes cretinism, which may include intellectual disability, deaf-mutism, difficulty walking, short stature, and sometimes hypothyroidism.

Diagnosis

• Assessment of thyroid structure and function

Diagnosis in adults and children is usually based on thyroid function, examination for goiter, and imaging tests identifying abnormalities in thyroid function and structure (see p. 776). All neonates should be screened by measuring the TSH level.

Treatment

• Iodide with or without levothyroxine

Infants with iodine deficiency are given L-thyroxine 3 µg/kg po once/day for a week plus iodide 50 to 90 µg po once/day for several weeks to quickly restore a euthyroid state. Children are treated with iodide 90 to 120 µg once/day. Adults are given iodide 150 µg once/day. Iodine deficiency can also be treated by giving levothyroxine. Serum TSH levels are monitored in all patients until the levels are normal (ie, < 5 µIU/mL).

Iodine Toxicity

Chronic toxicity may develop when intake is > 1.1 mg/day. Most people who ingest excess amounts of iodine remain euthyroid. Some people who ingest excess amounts of iodine, particularly those who were previously deficient, develop hyperthyroidism (Jod-Basedow phenomenon). Paradoxically, excess uptake of iodine by the thyroid may inhibit thyroid hormone synthesis (called Wolff-Chaikoff effect). Thus, iodine toxicity can eventually cause iodide goiter, hypothyroidism, or myxedema. Very large amounts of iodide may cause a brassy taste in the mouth, increased salivation, GI irritation, and acneiform skin lesions. Patients exposed to frequent large amounts of radiographic contrast dyes or the drug amiodarone also need to have their thyroid function monitored.

Diagnosis is usually based on thyroid function and imaging test findings (see p. 776), which are correlated with clinical data. Iodine excretion may be more specific but is not usually measured. Treatment consists of correcting thyroid abnormalities and, if intake is excessive, dietary modification.

Iron

Iron (Fe) is a component of hemoglobin, myoglobin, and many enzymes in the body. Heme iron, contained mainly in animal products, is absorbed much better than nonheme iron (eg, in plants and grains), which accounts for > 85% of iron in the average diet. However, absorption of nonheme iron is increased when it is consumed with animal protein and vitamin C.

Deficiency: Iron deficiency is one of the most common mineral deficiencies in the world. It may result from the following:

• Inadequate iron intake, common in infants, adolescent girls, and pregnant women

• Malabsorption (eg, celiac sprue)

• Chronic bleeding

Chronic bleeding due to colon cancer is a serious cause in middle-aged people and the elderly.

When deficiency is advanced, microcytic anemia develops (see p. 924).

In addition to anemia, iron deficiency may cause pica (a craving for nonfoods) and spoon nails and is associated with restless leg syndrome. Rarely, iron deficiency causes dysphagia due to postcricoid esophageal web.

Diagnosis involves CBC, serum ferritin, and possibly measurement of transferrin saturation (iron capacity).

All people with moderate or severe iron deficiency and some people with mild deficiency require iron supplementation.

Toxicity: Iron may accumulate in the body because of

• Iron therapy given in excessive amounts or for too long

• Repeated blood transfusions

• Chronic alcoholism

• Overdose of iron

Iron overload can also result from an inherited iron overload disease (hemochromatosis—see p. 1032), a potentially fatal but easily treatable genetic disorder in which too much iron is absorbed. Hemochromatosis affects > 1 million Americans.

An overdose of iron is toxic (see p. 3341), causing vomiting, diarrhea, and damage to the intestine and other organs.

Diagnosis is similar to that for iron deficiency.

Treatment often involves deferoxamine, which binds with iron and is excreted in urine.

Manganese

Manganese (Mn), necessary for healthy bone structure, is a component of several enzyme systems, including manganese-specific glycosyltransferases and phosphoenolpyruvate carboxykinase. Median intake is between 1.6 and 2.3 mg/day; absorption is 5 to 10%.

Deficiency has not been conclusively documented, although one experimental case in a volunteer resulted in transient dermatitis, hypocholesterolemia, and increased alkaline phosphatase levels.

Toxicity is usually limited to people who mine and refine ore; prolonged exposure causes neurologic symptoms resembling those of parkinsonism or Wilson's disease.

Molybdenum

Molybdenum (Mo) is a component of coenzymes necessary for the activity of xanthine oxidase, sulfite oxidase, and aldehyde oxidase.

Genetic and nutritional deficiencies of molybdenum have been reported but are rare. Genetic sulfite oxidase deficiency was described in 1967 in a child. It resulted from the inability to form the molybdenum coenzyme despite the presence of adequate molybdenum. The deficiency caused intellectual disability, seizures, opisthotonus, and lens dislocation.

Molybdenum deficiency resulting in sulfite toxicity occurred in a patient receiving long-term TPN. Symptoms were tachycardia, tachypnea, headache, nausea, vomiting, and coma. Laboratory tests showed high levels of sulfite and xanthine and low levels of sulfate and uric acid in the blood and urine. Ammonium molybdate 300 µg/day IV caused dramatic recovery.

A case of molybdenum toxicity may have occurred in 1961; it caused goutlike symptoms and abnormalities of the GI tract, liver, and kidneys.

Selenium

Selenium (Se) is a part of the enzyme glutathione peroxidase, which metabolizes hydro-peroxides formed from polyunsaturated fatty acids. Selenium is also a part of the enzymes that deiodinate thyroid hormones. Generally, selenium acts as an antioxidant that works with vitamin E. Some epidemiologic studies associate low selenium levels with cancer. In children with Down syndrome, selenium supplements may help prevent bacterial infections. Plasma levels vary from 8 to 25 µg/dL, depending on selenium intake. Diagnosis is usually clinical; sometimes blood glutathione peroxidase is measured.

Deficiency: Deficiency is rare, even in New Zealand and Finland, where selenium intake is 30 to 50 µg/day, compared with 100 to 250 µg/day in the US and Canada. In certain areas of China, where intake averages 10 to 15 µg/day, selenium deficiency predisposes patients to Keshan disease, an endemic viral cardiomyopathy affecting primarily children and young women. This cardiomyopathy can be prevented but not cured by sodium selenite supplements of 50 µg/day po. Patients receiving long-term TPN have developed selenium deficiency with muscle pain and tenderness that responded to a selenomethionine supplement. In Siberian Russia and China, growing children with selenium deficiency may develop chronic osteoarthropathy (Kashin-Beck disease). Selenium deficiency may contribute synergistically with iodine deficiency to the development of goiter and hypothyroidism.

Diagnosis is made clinically or sometimes by measuring glutathione peroxidase activity or plasma selenium, but neither of these tests is readily available. Treatment consists of sodium selenite 100 µg/day po.

Toxicity: At high doses (> 900 µg/day), selenium causes toxicity. Manifestations include hair loss, abnormal nails, dermatitis, peripheral neuropathy, nausea, diarrhea, fatigue, irritability, and a garlic odor of the breath. Toxic levels of plasma selenium are not well defined.

Zinc

Zinc (Zn) is contained mainly in bones, teeth, hair, skin, liver, muscle, leukocytes, and testes. Zinc is a component of several hundred enzymes, including many nicotinamide adenine dinucleotide (NADH) dehydrogenases, RNA and DNA polymerases, and DNA transcription factors as well as alkaline phosphatase, superoxide dismutase, and carbonic anhydrase. A diet high in fiber and phytate (eg, in whole-grain bread) reduces zinc absorption.

Deficiency: Dietary deficiency is unlikely in healthy people. Secondary zinc deficiency can develop in the following:

- Some patients with hepatic insufficiency (because the ability to retain zinc is lost)
- Patients taking diuretics
- Patients with diabetes mellitus, sickle cell disease, chronic renal failure, or malabsorption
- Patients with stressful conditions (eg, sepsis, burns, head injury)
- Elderly institutionalized and homebound patients (common)

Maternal zinc deficiency may cause fetal malformations and low birth weight.

Zinc deficiency in children causes impaired growth and impaired taste (hypogeusia). Other symptoms and signs in children include delayed sexual maturation and hypogonadism. In children or adults, symptoms include hypogonadism, alopecia, impaired immunity, anorexia, dermatitis, night blindness, anemia, lethargy, and impaired wound healing.

Zinc deficiency should be suspected in undernourished patients with typical symptoms or signs. However, because many of the symptoms and signs are nonspecific, clinical diagnosis of mild zinc deficiency is difficult. Laboratory diagnosis is also difficult. Low albumin levels, common in zinc deficiency, make serum zinc levels difficult to interpret; diagnosis usually requires the combination of low levels of zinc in serum and increased urinary zinc excretion. If available, isotope studies can measure zinc status more accurately.

Treatment consists of elemental zinc 15 to 120 mg/day po until symptoms and signs resolve.

Acrodermatitis enteropathica (a rare, once fatal autosomal recessive disorder) causes malabsorption of zinc. Psoriasiform dermatitis develops around the eyes, nose, and mouth; on the buttocks; and in an acral distribution. The disorder also causes hair loss, paronychia, impaired immunity, recurrent infection, impaired growth, and diarrhea. Symptoms and signs usually develop after infants are weaned from breast milk. In such cases, doctors suspect the diagnosis. If deficiency is diagnosed, zinc sulfate 30 to 150 mg/day po usually results in complete remission.

Toxicity: The recommended upper limit for zinc intake is 40 mg/day. Toxicity is rare. Ingesting doses of elemental zinc ranging from 100 to 150 mg/day for prolonged periods interferes with copper metabolism and causes low blood copper levels, RBC microcytosis, neutropenia, and impaired immunity; higher doses should be given only for short periods of time and the patient should be followed closely. Ingesting larger amounts (200 to 800 mg/day), usually by consuming acidic food or drink from a galvanized (zinc-coated) container, can cause anorexia, vomiting, and diarrhea. Metal fume fever, also called brass-founders' ague or zinc shakes, is caused by inhaling industrial zinc oxide fumes; it results in neurologic damage. Symptoms usually resolve after 12 to 24 h in a zinc-free environment.

Chapter 6. Obesity and the Metabolic Syndrome

Obesity

Obesity is excess body fat; consequences depend not only on the absolute amount but also on the distribution of the fat. Complications include cardiovascular disorders, diabetes mellitus, many cancers, cholelithiasis, fatty liver and cirrhosis, osteoarthritis, reproductive disorders in men and women, psychologic disorders, and premature death. Diagnosis is based on body mass index (BMI—calculated from height and weight) and waist circumference. BP, fasting plasma glucose, and lipid levels should be measured. Treatment includes physical activity, dietary and behavioral modification, and sometimes drugs or surgery.

Prevalence of obesity in the US is high and is increasing, particularly among children and adolescents (see Table 6-1).

Prevalence is more than twice as high at age 55 as at age 20. Obesity is twice as common among women in a lower socioeconomic group as among those in a higher group. Prevalence among black and white men does not differ significantly, but it is higher among black women than white women. More than 50% of black women ≥ 40 yr are obese; > 80% are overweight.

In the US, obesity and its complications cause as many as 300,000 premature deaths each year, making it second only to cigarette smoking as a preventable cause of death.

[**Table 6-1.** Changes in Prevalence of Obesity According to Nhanes]

Etiology

Almost all cases of obesity result from a combination of genetic predisposition and a chronic imbalance between energy intake, energy utilization for basic metabolic processes, and energy expenditure from physical activity.

Genetic factors: Heritability of BMI is about 66%. Genetic factors may affect the many signaling molecules and receptors used by parts of the hypothalamus and GI tract to regulate food intake (see Sidebar 6-1). Rarely, obesity results from abnormal levels of peptides that regulate food intake (eg, leptin) or abnormalities in their receptors (eg, melanocortin-4 receptor).

Genetic factors also regulate energy expenditure, including BMR, diet-induced thermogenesis, and nonvoluntary activity-associated thermogenesis. Genetic factors may have a greater effect on the distribution of body fat, particularly abdominal fat (see Metabolic Syndrome on p. 64), than on the amount of body fat.

Environmental factors: Weight is gained when caloric intake exceeds energy needs. Important determinants of energy intake include portion sizes and the energy density of the food. High-fat foods, processed foods, and diets high in refined carbohydrates, soft drinks, fruit juices, and alcohol promote weight gain. Diets high in fresh fruit and vegetables, fiber, and complex carbohydrates, with water as the main fluid consumed, minimize weight gain. A sedentary lifestyle promotes weight gain.

Regulatory factors: Prenatal maternal obesity, prenatal maternal smoking, intrauterine growth restriction, and insufficient sleep can disturb weight regulation. About 15% of women permanently gain ≥ 20 lb with each pregnancy. Obesity that persists beyond early childhood makes weight loss in later life more difficult.

Drugs, including corticosteroids, lithium, traditional antidepressants (tricyclics, tetracyclics, and monoamine oxidase inhibitors [MAOIs]), benzodiazepines, and antipsychotic drugs, often cause weight gain.

Uncommonly, weight gain is caused by one of the following disorders: