PART VIII

Nutritional Problems and Deficiency Diseases

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129 General Principles

Benjamin Caballero

Nutritional problems in tropical areas are almost always associated with deficiency states, with protein-energy malnutrition, hypovitaminosis A, and iron and iodine deficiencies being the most prevalent. According to UN organizations' data, around 20% of the world population consumes amounts of foods insufficient to sustain health and an active and productive life. One of every three children exhibits growth delay, and more than 40% of women are anemic. The vast majority of these populations are found in tropical and other developing regions.

Although acute food shortages caused by civil war, drought, or natural disasters periodically and recurrently affect millions of people, particularly in Africa, the number of individuals taking in insufficient amounts of dietary energy has declined over the past 15 years, from 1 billion in 1975 to less than 800 million in 1990. Most of the improvement reflects advances in South Asia, because trends have worsened in the African continent.

Insufficient dietary intake of protein, energy, and/or micronutrients is only one factor leading to nutritional diseases in the tropics. The unsanitary environment leads to frequent infections of the gastrointestinal tract, which, even if relatively minor, cause malabsorption of essential nutrients. A child living in an unsanitary environment can have as many as ten or more episodes of acute gastroenteritis in a year. Each episode leads to a negative balance between intake and losses, with consequent weight loss and delay in longitudinal growth. Children who survive recurring illnesses early in life may never recover from their growth delay, becoming permanently stunted adults. Conversely, an impaired nutritional status increases the risk of infection by affecting the immune system, facilitating bacterial colonization, or increasing the frequency and severity of infectious illnesses.

Many children living in a highly contaminated environment exhibit a state of chronic immune stimulation, characterized by increased production of acute-phase reactants, e.g., C-reactive protein, fibrinogen, acid α-glycoprotein, and others. The nutritional cost of mounting such a response has been the focus of interest. The need for certain essential amino acids to synthesize these acute-phase proteins may result in an increased breakdown of skeletal muscle protein, further impairing growth.

A second factor adversely affecting the utilization of dietary nutrients is the composition of the typical diet in many developing countries. Diets based on cereals and grains tend to have a high content of substances such as phytate, which inhibit the absorption of essential minerals. Some vegetable-based diets may also contain antithyroid factors or other elements interfering with the metabolism and utilization of essential nutrients.

Some of the classic manifestations of vitamin deficiencies can still be identified in refugee camps and in extreme conditions of food scarcity. Outbreaks of beriberi, scurvy, and pellagra have occurred among populations displaced by civil war. Iron deficiency constitutes the most common single-nutrient deficiency in the world and, along with the deficiency of vitamin B_{12} and folic acid, is responsible for the widespread occurrence of anemia in children and pregnant women.

A special section is dedicated to the important issue of the interaction between nutrition and infection. Also, the unique characteristics of the tropical neuropathies, many of them associated with vitamin deficiencies, are discussed in a separate chapter. The nervous system is extremely sensitive to the supply of certain vitamins, and their absence or severe depletion in the diet may lead to rapid damage of the central and peripheral nervous systems' components, which sometimes can be irreversible.

Although nutritional deficiencies are by far the most common in developing countries, there is an increasing trend, particularly in urban areas, toward diseases commonly associated with excess—such as obesity, diabetes, and cardiovascular disease. The rapid migration to the cities produces drastic changes in lifestyle and food choices in children and adults. Energy expenditure for physical activity is reduced owing to a more sedentary way of life, and more "empty" calories and processed foods are consumed; although the diet may still be marginal in certain nutrients, it is likely to contain more calories from fat, including more saturated fats. As a consequence, stunting in linear growth and excess body fat can be observed in many children in the poor slums of large urban areas in developing countries. The long-term impact of these transitional conditions is unclear, but their increasing prevalence will pose a challenge to the primary health care system, which has been historically focused on the management of nutritional deficiencies.

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130 Protein-Energy Malnutrition

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Protein-energy malnutrition (PEM) is the most important nutritional disease in developing countries because of its high prevalence and its relationship with child mortality rates, impaired growth and development, decreased work capacity, and inadequate social and economic improvement. Fifty-six percent of deaths among children 6 to 59 months old in 53 developing countries have been attributed to malnutrition's potentiating effects in infectious diseases, and mild and moderate malnutrition were involved in 83% of those deaths.

PEM results when the body's needs for protein, energy

fuels (calories), or both cannot be satisfied by the diet. It is usually associated with mineral and vitamin deficits, but the clinical and metabolic alterations of energy and/or protein deficiency predominate. PEM covers the severe clinical syndromes of kwashiorkor (edematous, predominant protein deficiency), marasmus (nonedematous, predominant energy deficiency) or marasmic kwashiorkor (edematous combination of chronic energy deficiency and acute or chronic protein deficit), and the much more numerous mild and moderate cases. The term *malnutrition* is usually used in lay language for PEM.

PEM can be primary in origin, when it is the direct result of inadequate food intake, or secondary, when it is the result of other diseases that lead to low food ingestion, inadequate nutrient absorption or utilization, increased nutritional requirements, and/or increased nutrient losses. Although PEM is mainly a problem in early childhood, it can occur in older children and adults, but severe degrees of primary PEM are rare outside early childhood, except in famine conditions.

HISTORY. The cause of edematous PEM was not understood for a long time because it could be found among children who were not starving and among families in good socioeconomic position. It was initially believed to be caused by tropical parasites or vitamin deficiencies, because of the skin lesions. The real nature of the disease was studied more carefully after Cicely Williams' descriptions in the mid-1930s of kwashiorkor. This term, used by the Ga tribe in the Gold Coast (now Ghana) for "the sickness the older child gets when the next baby is born," already suggested that the disease could be associated with an inadequate diet during the weaning period. Pediatricians who worked in tropical countries showed that the edematous disease could be cured by feeding milk or other high-protein foods. In the 1940s, researchers showed that most patients had low concentrations of serum proteins and that this could also be related to the quality of dietary proteins. By the 1950s, more than 40 names had been given to this clinical syndrome. Some of them, e.g., *infantile pluricarential syndrome*, indicated that young children were mainly affected and that a deficit of various nutrients was involved. Others, e.g., *Mehlnahrschade* ("damage by cereal flours"), *starch edema*, and *sugar babies*, indicated that it was caused by the intake of foods with high carbohydrate and low protein contents. Today, the more comprehensive term of *protein-energy* (or *protein-calorie*) *malnutrition* is universally accepted, with edematous and nonedematous manifestations of its severe forms. In the past 30 years, it has been shown that marasmus and kwashiorkor have distinct metabolic features; that some manifestations, e.g., anemia and reduced physical activity, are partly a result of adaptive mechanisms; that the immune response of severely malnourished patients is impaired; and that physical and emotional stimulation are important elements in treating malnourished children. These findings form the basis for current therapeutic approaches.

ETIOLOGY

Biologic Factors

Maternal Malnutrition. This can lead to intrauterine malnutrition and low birth weight (Chapter 15). Lack of sufficient food to satisfy an infant's needs for catch-up results in infantile PEM. Diets with low concentrations of proteins and energy, e.g., overdiluted milk formulas and bulky vegetable foods, can lead to PEM in young children, whose gastric capacity limits the amount of food they can ingest, and in elderly persons with anorexia or difficulty in eating without assistance. Diets poor in protein and rich in carbohydrates are particularly likely to produce kwashiorkor.

Infectious Diseases. These are major contributing and precipitating factors in PEM (Chapter 133.1). Diarrheal disease, measles, AIDS, tuberculosis, malaria, and other infections frequently result in negative protein and energy balance owing to poor appetite, vomiting, impaired absorption, and increased catabolic processes. Intestinal parasites have little or no effect unless the infection is extensive and causes anemia or diarrhea (Chapter 133.2).

Social and Economic Factors. Poverty is frequently associated with PEM because of low food availability, overcrowded and unsanitary living conditions, and improper child care. *Ignorance* leads to poor child-rearing practices, misconceptions about the use of certain foods, inadequate feeding procedures during illnesses, and improper food distribution within the family members. A decline in the practice and duration of breast-feeding, combined with inadequate weaning practices, is related to increasing rates of infantile PEM.

Social problems e.g., child abuse, maternal deprivation, abandonment of the elderly, alcoholism, and drug addiction can result in PEM. Cultural and social practices that impose food taboos, some food and diet fads, and the migration from traditional rural settings to urban slums also contribute to the appearance of PEM.

Environmental Factors. Overcrowded and/or unsanitary living conditions lead to frequent infections. Droughts, floods, wars, and forced migrations lead to cyclic, sudden, or prolonged food scarcities and can cause PEM among whole populations (Chapter 19). Postharvest losses of food due to bad storage conditions and inadequate food distribution systems contribute to PEM, even after periods of agricultural plenty.

EPIDEMIOLOGY. There are about 840 million undernourished people in the world, most of them in developing countries: about 30% each in southern and eastern Asia, 25% in sub-Saharan Africa, and 8% in Latin America and the Caribbean. Because of this, 36% (210 million) of the children <5 years old in the developing world are underweight (low weight for age), 43% (250 million) are stunted (low height for age), and 9% (52 million) are wasted (low weight for height). This prevalence ranges from 12% underweight, 22% stunted, and 3% wasted in Latin America and the Middle East to 62% underweight, 61% stunted, and 17% wasted in southern Asia. When countries are not disturbed by natural and manmade disasters, e.g., droughts, land wastage, wars, and economic crisis, the trend is for a gradual improvement in the prevalence of child malnutrition.

In industralized countries, primary PEM is encountered mainly among young children of the lower socioeconomic groups, the elderly who live alone, and adults addicted to alcohol and drugs.

Age and Physiologic Conditions

Infants and Young Children. PEM is more frequent among infants and young children because growth increases their nutritional requirements, they cannot obtain food by their own means, and, when living under poor hygienic conditions, they frequently become ill with diarrhea and other infections. Infants who are weaned prematurely from the breast or who are breast-fed for a prolonged time without adequate complementary feeding practices become malnourished for lack of adequate energy and protein intake.

Prolonged intake of insufficient food can result in marasmus, which is the most common form of severe PEM before 1 year of age. Kwashiorkor, the edematous form of the disease, is more frequent after 18 months of age and typically occurs in children with diets consisting of starchy gruels, diluted cereal-based beverages, and vegetable foods rich in carbohydrates but almost devoid of proteins of good nutritional quality (i.e., lacking one or more essential amino acids). Most often, the severe protein deficit is associated with chronic dietary energy deficit and results in a combined

form of marasmic kwashiorkor. The appearance of edema is frequently preceded or accompanied by acute diarrhea or another infectious disease.

Older Children and Adults at High Risk. These usually have milder forms of PEM because they can cope better with social and food availability constraints. Infections and other precipitating factors become less severe, and early survival may imply a natural selection of the more fit. Pregnant and lactating women can also have PEM as a result of the increases in their nutritional requirements. However, the consequences of the dietary deficiencies affect mainly the growth, nutritional status, and survival rates of their fetuses, newborn babies, and infants. Elderly persons who are unable to care properly for themselves tend to suffer from PEM. Gastrointestinal alterations can be an important contributing factor.

Adolescents, adult men, and nonpregnant, nonlactating women usually have the lowest prevalence and the mildest forms of the disease because of greater opportunities to obtain food and cultural practices that protect the productive members of the family. Severe primary PEM occurs among them in conditions of extreme privation and famine and in situations of social or chemical dependence without adequate nutritional support, as may be the case with patients with mental disabilities, prisoners, alcoholic individuals, and those addicted to drugs. Severe PEM is seen more frequently in adults as secondary to other illnesses, e.g., chronic infections, cancer, AIDS, malabsorption, and liver and endocrine diseases. In such cases, both the malnutrition and the underlying cause must be treated.

PATHOPHYSIOLOGY AND ADAPTIVE RESPONSES. PEM develops gradually in weeks or months, allowing for metabolic and behavioral adjustments. This results in decreased nutrient demands and a nutritional equilibrium compatible with a lower level of cellular nutrient availability. If the supply of nutrients becomes persistently lower, patients can no longer adapt and may even die. Metabolic disruptions can be due to severe nutrient deficit, complications (e.g., infections), or inadequate treatment (e.g., abrupt administration of large amounts of dietary energy or protein). Patients whose PEM develops slowly—as is usually the case in marasmus—are better adapted to their current nutritional status and maintain a less fragile metabolic equilibrium than those with more acute PEM, as in kwashiorkor of rapid onset.

Energy Mobilization and Expenditure. A decrease in energy intake is followed by a decrease in energy expenditure, accounting for shorter periods of play and physical activity in children and for longer rest periods and less physical work in adults. When the decrease in energy expenditure cannot compensate for the insufficient intake, body fat is mobilized, with a decrease in adiposity and weight loss. Lean body mass diminishes at a slower rate. As the cumulative energy deficit becomes more severe, subcutaneous fat is markedly reduced and protein catabolism leads to muscle wasting.

Protein Metabolism. Metabolic adaptations tend to spare visceral protein and preserve essential protein-dependent functions, more so in marasmus than in kwashiorkor. Enzymatic changes favor muscle protein breakdown and liver protein synthesis, as well as energy mobilization from fat depots. Some visceral protein is lost in the early development of PEM but then becomes stable until the nonessential tissue proteins are depleted; the loss of visceral protein then increases, and death may be imminent unless nutritional therapy is successfully instituted.

The half-life of albumin increases, and a shift from the extravascular to the intravascular pool assists in maintaining adequate levels of circulating albumin. When protein depletion becomes too severe or is complicated by a systemic infection, the adaptive mechanisms fail and the concentration of serum proteins, especially albumin, decreases. The ensuing reduction in intravascular oncotic pressure and the outflow of water into the extravascular space contribute to the development of the edema of kwashiorkor.

Endocrine Functions. In severe PEM there is a marked decrease in activity of hormones involved in building body reserves, increasing metabolism and enhancing nonvital growth-related functions, e.g., insulin, IGF-1, thyroid hormones, and gonadotropin. There is a normal or increased activity of glucocorticoids, which favor muscle protein catabolism, lipolysis, and gluconeogenesis. The functional capacities of the hypothalamic-pituitary axis and adrenal medulla are preserved, thus allowing endocrine and metabolic responses to stress conditions. Some investigators have postulated that the evolution of PEM into either kwashiorkor or marasmus may be partly related to differences in adrenocortical response, in which the better response preserves visceral proteins more efficiently and leads to the better-adapted syndrome of marasmus.

Hematology and Oxygen Transport. The reduction in lean body mass and the lower physical activity of malnourished patients lead to lower oxygen demands. The simultaneous decrease in dietary amino acids results in reduced hematopoietic activity, which spares amino acids for synthesis of other more necessary body proteins. As long as the tissues' needs for oxygen are satisfied by the existing capacity for oxygen transport, the reduction in hemoglobin concentration should be considered an adaptive response and not a functional anemia (i.e., with tissue hypoxia). Although the level of circulating hemoglobin is usually low, severely malnourished patients may have relatively high body iron stores and may retain the ability to produce erythropoietin and reticulocytes in response to acute hypoxia. Nevertheless, these patients are prone to develop functional, severe anemia if they have a superimposed dietary deficiency of iron or folic acid or chronic blood loss, as in hookworm infection.

When tissue synthesis, lean body mass, and physical activity begin improving with dietary treatment, a rise in oxygen demands follows, calling for accelerated hematopoiesis. If iron (Chapter 132.1), folic acid, and vitamin B_{12} (Chapter 131.7) are not available in sufficient amounts, functional anemia with tissue hypoxia develops. On the other hand, administration of hematinics to severely malnourished patients induces a hematopoietic response only after dietary treatment produces an increase in lean body mass (Fig. 130–1).

Cardiovascular and Renal Functions. Central circulation takes precedence over peripheral circulation, which accounts for the cool hands and feet in severe PEM. Cardiac output and blood pressure decrease, and cardiovascular reflexes are altered, leading to postural hypotension and diminished venous return. Hemodynamic compensation results mainly from tachycardia. In severe PEM, peripheral circulatory failure comparable to hypovolemic shock may occur. Renal plasma flow and glomerular filtration rates may be reduced as a consequence of the decreased cardiac output, but water clearance and the ability to concentrate and acidify urine are not impaired.

Immune System and Monokine Metabolism. Malnourished patients have a greater predisposition to infections, which tend to be more prolonged and severe than in well-nourished individuals (Chapter 133.1). In severe PEM there is a decrease in T lymphocytes and in complement and opsonic activities, thus explaining the high susceptibility to gram-negative bacterial sepsis. The synthesis and activity of interleukin-1 are depressed, and this decrement contributes to the poor febrile response and low leukocyte count in infection. On the other hand, cachectin or tumor necrosis factor increases, and this

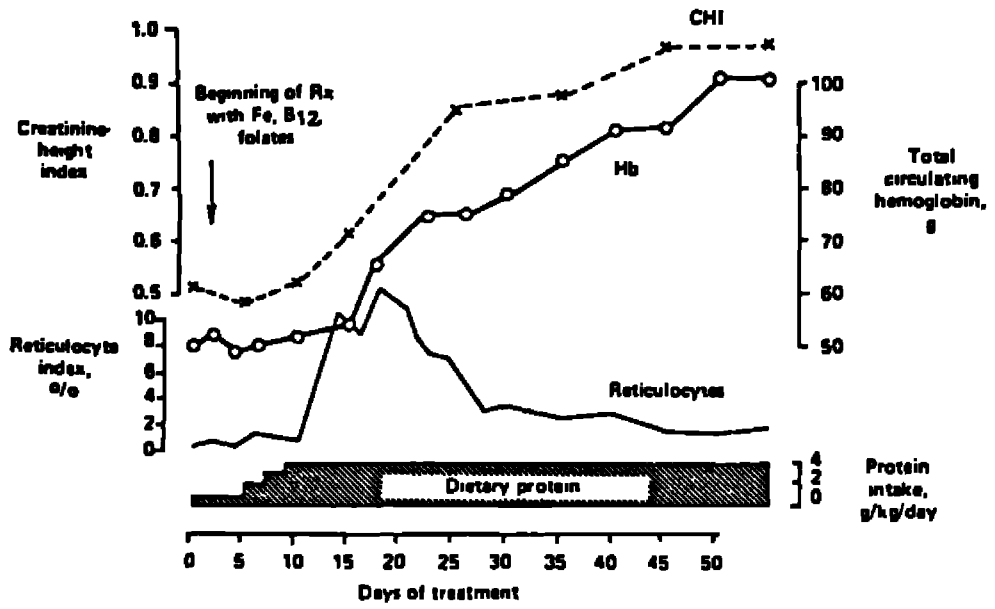

Figure 130–1. Hematologic response of a child with severe protein-energy malnutrition. Treatment with iron, folic acid, and vitamin B_{12} began at an unnecessarily early time, on day 2; dietary energy and proteins were increased gradually to 150 kcal (630 KJ) and 4 g protein/kg/day on day 9. Reticulocyte and hemoglobin response occurred until lean body mass began increasing, as assessed by the creatinine-height index (CHI). (From Torun B, Chew F: *In* Shils ME, Olson JA, Shike M [eds]: Modern Nutrition in Health and Disease, 8th ed. Philadelphia, Lea & Febiger, 1994.)

increase could contribute to the anorexia, muscle wasting, and lipid abnormalities of severe PEM.

Electrolytes. The cellular exchange of sodium and potassium is altered in severe PEM, leading to potassium loss and increased intracellular sodium. The latter may lead to intracellular overhydration. Total body potassium decreases because of the reduction in muscle proteins and loss of intracellular potassium. These alterations contribute to the increased fatigability and reduced strength of skeletal muscle and to the reduced motility of intestinal muscle.

Gastrointestinal Functions. In severe PEM there is a decrease in disaccharidase activity, in gastric and pancreatic secretions, and in bile production, which impair digestion and absorption of carbohydrates, lipids, and amino acids. However, ingestion of nutrients in high therapeutic amounts usually allows for their uptake in sufficient quantity to permit nutritional recovery. Nevertheless, malnourished persons are prone to diarrhea because of these alterations and because of irregular intestinal motility and gastrointestinal bacterial overgrowth. This tends to disappear with nutritional recovery. Normal intestinal absorption is also restored with nutritional recovery, unless there is an underlying food or nutrient intolerance unrelated to primary PEM.

Central and Peripheral Nervous System. Severe PEM at an early age may reduce or delay brain growth, nerve myelination, neurotransmitter production, and velocity of nervous conduction. The long-term functional implications of these alterations have not been clearly demonstrated in humans, because it is impossible to separate nutrition from other factors that can affect motor skills, intelligence, and behavior. The quality of nutritional rehabilitation and psychosocial support, the degree of stimulation by family members, and other environmental factors influence the developmental outcome of a malnourished child.

Other Factors Leading to Kwashiorkor. In addition to a diet deficient in proteins and with a low protein:energy ratio and to the hypothesis related to differences in adrenocortical response, other theories involve the production and disposal of free radicals, metabolic shunts due to infection, and aflatoxin poisoning. The toxic effects of free radicals would be responsible for cell damage leading to edema, fatty liver, and skin lesions. Among the factors that may increase free radicals are infections, toxins, and excessive exposure to iron. Their formation is decreased by the antioxidant function of vitamins A (or beta-carotene), C, and E and by the proteins ceruloplasmin and transferrin, which bind free iron and favor its oxidation. Free radicals and the peroxides they generate are removed through reactions catalyzed by enzymes that contain Cu, Zn, Mn, or Se. However, none of these theories has been proved. Furthermore, the pathogenesis of edematous PEM may not be a single entity, and its causes may differ in accordance with the age of the patients, multiple nutritional deficiencies, and other concomitant conditions.

Disruption of Adaptation. Severe energy deficiency can lead to a serious decompensation causing hypoglycemia, hypothermia, impaired circulatory and renal functions, acidosis, coma, and death. Metabolic decompensation due to severe protein deficiency produces loss of visceral protein and function, hemorrhagic diathesis, jaundice, impaired cardiac and renal functions, water and sodium retention, pulmonary congestion, increased susceptibility to pulmonary infections, coma, and death.

Inadequate dietary management of severely malnourished patients can cause serious metabolic disruption with fatal consequences. This includes premature introduction of a high-energy or high-protein diet. Abrupt administration of too much protein to patients, especially with edematous PEM, as well as large or rapid transfusions of blood or plasma, can result in a swift increase in intravascular protein concentration and entry of extracellular fluid into the vascular compartment, leading to heart failure and pulmonary edema.

Infections can produce serious metabolic disruptions due to enhanced protein catabolism and nitrogen losses, diversion of nitrogen metabolism to the synthesis of acute phase proteins, impaired energy metabolism, and/or production of free radicals.

DIAGNOSIS AND CLINICAL MANIFESTATIONS. Weight loss and delayed growth are the only practical diagnostic indicators in the early stages of PEM. Other clinical manifestations usually do not appear until the disease is well advanced, and they vary according to the severity of the disease, the patient's age, the presence of other nutritional deficits or infection, and the predominance of energy or protein deficiency. Some functional indicators, e.g., decrease in physical activity, immunologic alterations, and behavioral changes, appear early, but their quantitative assessment is not yet well standardized or is too complex for routine use. Dietary history of individual patients, dietary surveys in population groups, and information on dietary habits and food availability help to appraise the risk of PEM and to interpret anthropometric and clinical findings.

Anthropometric Measurements. Several anthropometric measurements and indexes have been used to diagnose and classify PEM. The choice of measurement depends on simplicity, accuracy, and sensitivity, as well as on the availability of measuring instruments and the existence of reference standards for interpretation.

The best assessment is based on measurements of (1) weight and height or length, to calculate weight for height of infants and young children, and body mass index (BMI = weight in kg/height^2 in meters) of school-age children, adolescents, and adults, as indexes of current nutritional status; and (2) records of age, to calculate height for age, as an index of past nutritional history. When the exact age is not known, assessment of reasonably reliable information may be attempted by constructing a local events calendar.

Those indexes can be interpreted by comparing them with data derived from the U.S. National Center for Health Statistics, as recommended by the World Health Organization

TABLE 130–1. Classification of Current (Wasting) and Past or Chronic (Stunting) PEM in Infants and Children, Based on Weight for Height and Height for Age*

	Normal	Mild	Moderate	Severe
Weight for height (deficit = wasting)	±1 Z (91–110%)	−1.1 to −2 Z (81–90%)	−2.1 to −3 Z (76–80%)	< −3 Z (<76%) or with edema
Height for age (deficit = stunting)	≥−1 Z (≥96%)†	−1.1 to −2 Z (91–95%)	−2.1 to −3 Z (86–90%)	< −3 Z (<86%)

*Standard deviations from the NCHS/WHO median, or Z scores. Percent ranges in relation to the median (in parentheses) were rounded to the multiple of 5 that approximates the corresponding Z scores for children between 6 months and 5 years old.
†Upper normal limits of height for age have not been established.

(WHO). The advantages of using this universal reference outweigh its disadvantages and the limitations of reliable normal local references. The term *wasting* is used for a deficit in weight for height or BMI, and *stunting* for a deficit in height for age. Patients may then fall into four categories: (1) normal, (2) wasted but not stunted (suffering from acute PEM), (3) wasted and stunted (suffering from acute and past or chronic PEM), and (4) stunted but not wasted (past PEM with present adequate nutrition, or nutritional dwarfs).

The severity of wasting and stunting can be graded by calculating weight as a percentage of the reference median weight for height, and height as a percentage of the reference median height for age, as follows:

$$\frac{\%\text{ wt for ht}}{(\text{or ht for age})} = \frac{\text{observed wt (or ht)}}{\text{reference wt for patient's ht (or ht for patient's age)}} \times 100$$

Percent deviations from the median are easier to understand by the general public and to calculate by fieldworkers, although standard deviations from the median (Z scores) and centiles are statistically more adequate. The classification shown in Table 130–1 is suggested for most countries, although some might find it convenient to use different cutoff points for specific groups. For example, <95% of the reference height for age might be acceptable in populations that are genetically short. Color-coded charts and graphs, e.g., those devised by Nabarro and McNab, can simplify the measurement and interpretation of weight for height in infants and children.

Weight for age is useful for epidemiologic purposes, but in clinical use it does not differentiate between a truly underweight child (current PEM) and one who is short in stature but well proportioned in weight (past PEM).

Table 130–2 shows the classification of adult PEM based on BMI. For simplicity, the same BMI criteria are suggested to classify males and females. For adolescents, interpretation of BMI must take into account age and sexual maturation. If age- and maturation-specific references are not available, it is suggested that the diagnosis of PEM in adolescent boys and girls be based on a BMI <15.0 at ages 11 to 13 years, and <16.5 at ages 14 to 17 years. The corresponding values for severe PEM would be <13.0 and <14.5, respectively.

TABLE 130–2. Classification of Protein-Energy Malnutrition in Adult Men and Women

Body Mass Index (BMI)*	PEM
≥18.5	Normal
17.0–18.4	Mild
16.0–16.9	Moderate
<16.0	Severe

*BMI = weight (kg)/height^2 (m).

Measurement of upper arm circumference has been advocated under field conditions without access to a weighing scale. It is not a sensitive index, but it allows identifying the more severely malnourished children who require urgent treatment.

Mild and Moderate PEM. The main feature is weight loss. Leanness with reduction in subcutaneous adipose tissue may be clinically evident in children and adults. As described earlier, weight for height and BMI are lower than the reference standards. Repeated measurements show a flattening of the weight-for-age curve or weight gains that follow a channel below the lower limit accepted for well-nourished children. This can also be seen in anthropometric community surveys. When PEM is chronic or endemic, children also show slower growth in height and they are stunted.

Children may become more sedentary, and capacity for prolonged physical work is reduced in adolescents and adults. Other nonspecific manifestations, especially among children, may include pallor, apathy, lack of liveliness, short attention span, and frequent episodes of diarrhea. Clinical laboratory tests are not helpful in diagnosing mild or moderate PEM.

Severe PEM. In addition to clinical features, dietary and clinical history are important for diagnosis. Marasmus is usually associated with severe food shortage, prolonged semistarvation, early weaning, or infrequent feeding of infants. Kwashiorkor is often associated with poor protein intake, late weaning, and present or recent episodes of acute diarrhea or measles. Chronic or recurrent diarrhea and infections are common features.

Marasmus. Generalized muscle wasting and absence of subcutaneous fat give patients with severe, nonedematous PEM a skin-and-bones appearance (Fig. 130–2). Marasmic patients frequently have 60% or less of the weight expected for their height, and children are markedly stunted. The hair is sparse, thin, and dry, without its normal sheen. The skin is dry and thin, with little elasticity, and it wrinkles easily. Patients are apathetic but usually aware and have a look of sadness or anxiety on their face. These features and the sunken cheeks caused by disappearance of subcutaneous fat give a marasmic child's face the appearance of a monkey's or an old person's face.

Some patients have no appetite, whereas others are ravenously hungry, but they seldom tolerate large amounts of food and they vomit easily. Weakness is marked, and children frequently cannot stand without help. Blood pressure and body temperature may be low, but tachycardia may be noted. Hypoglycemia can occur, especially after fasting for 6 or more hours, and is often accompanied by hypothermia of 35.5°C or less. The viscera are usually small. Abdominal distention may be present. The lymph nodes are easily palpable.

Common complicating features are acute gastroenteritis,

***Figure* 130–2.** Marasmus in a 5-month-old baby (West Indies). Note the generalized muscle wasting and absence of subcutaneous fat, the growth retardation, and the sparse hair.

dehydration, respiratory infections, and eye lesions due to hypovitaminosis A (Chapter 131.1). Systemic infections lead to septic shock or intravascular clotting with high mortality rates. Dietary history has an important role in the differential diagnosis from the secondary PEM of AIDS, tuberculosis, cancer, and other body-wasting diseases.

Kwashiorkor. The predominant feature is soft, pitting, painless edema, usually in the feet and legs but extending to the perineum, upper extremities, and face in severe cases (Fig. 130–3). Many patients have skin lesions, often confused with pellagra, in the areas of edema, continuous pressure (e.g., at the buttocks and back), or frequent irritation (e.g., in the perineum and thighs). The skin may be erythematous, and it glistens in the edematous regions with zones of dryness, hyperkeratosis, and hyperpigmentation, which tend to become confluent. The epidermis peels off in large scales, exposing underlying tissues that are easily infected. Subcutaneous fat is preserved, and there may be some muscle wasting. Weight deficit, after accounting for the weight of edema, is usually not as severe as in marasmus. Children may be stunted or of normal height, depending on the chronicity of the current episode and on past nutritional history.

Patients may be pale, with cold and cyanotic extremities. They are apathetic and irritable, cry easily, and have an expression of misery and sadness. Anorexia (sometimes necessitating nasogastric tube feeding), postprandial vomiting, and diarrhea are common. These conditions usually improve as nutritional recovery progresses, without specific gastrointestinal treatment. Hepatomegaly with a soft, round edge caused by severe fatty infiltration is often present. The abdomen is frequently protruding because of a distended stomach and intestinal loops. Peristalsis is irregular and frequently slow. Muscle tone and strength are greatly reduced. Tachycardia is common. Both hypothermia and hypoglycemia can occur after short periods of fasting.

The hair is dry, brittle, and without its normal sheen, and it can be pulled out easily without pain. Curly hair becomes straight, and the pigmentation usually changes to dull brown, red, or yellowish white. Alternating periods of poor and relatively good protein intake can produce bands of depigmented and normal hair, termed the *flag sign*.

The same complications occur as in marasmus, but diarrhea and respiratory and skin infections are more frequent and severe. Infections may occur without fever, tachycardia, respiratory distress, or leukocytosis. The most common causes of death are pulmonary edema with bronchopneumonia, septicemia, gastroenteritis, and water and electrolyte imbalances. Differential diagnosis must include other causes of edema and hypoproteinemia and secondary PEM due to impairment in protein absorption or metabolism.

Marasmic Kwashiorkor. This form of edematous PEM combines clinical characteristics of kwashiorkor and marasmus. The main features are the edema of kwashiorkor, with or

***Figure* 130–3.** Kwashiorkor in an 18-month-old child (Indonesia). Note the edema in the lower limbs, the wasted muscles with some subcutaneous fat present, the light sparse hair, the flaky dermatosis in the lower legs, and skin pallor (compared with mother). (Courtesy of the late Dr. H. A. P. C. Oomen.)

***Figure* 130–4.** Marasmic kwashiorkor in a 22-month-old child (Guatemala). Note the edema in the lower part of the body, the emaciated upper part, the marked stunting, and the skin lesions. (From Torun B, Viteri FE: *In* Warren KS, Mahmoud AAF [eds]: Tropical and Geographic Medicine, 2nd ed. New York, McGraw-Hill, 1990.)

without its skin lesions, and the muscle wasting and decreased subcutaneous fat of marasmus (Fig. 130–4). When edema disappears during early treatment, the patient's appearance resembles that of marasmus. Biochemical features of both marasmus and kwashiorkor are seen, but the alterations of severe protein deficiency usually predominate.

BIOCHEMICAL AND HISTOPATHOLOGIC FEATURES OF SEVERE PEM. These allow better understanding of the pathophysiology but have little practical importance in diagnosing the disease. *Treatment of severe PEM must not be delayed while awaiting laboratory results.*

Biochemical Abnormalities. The most common biochemical findings are as follows: (1) Serum concentrations of total proteins, especially albumin, are markedly reduced in edematous PEM and normal or moderately low in marasmus. (2) Hemoglobin and hematocrit are usually low, more so in kwashiorkor than in marasmus. (3) The ratio of nonessential to essential amino acids in plasma is elevated in kwashiorkor and usually normal in marasmus. (4) Serum levels of free fatty acids are elevated, particularly in kwashiorkor. (5) Blood glucose level is normal, but it may be low after fasting 6 or more hours. (6) Urinary excretions of creatinine, hydroxyproline, 3-methylhistidine, and urea nitrogen are low. Edematous children have markedly reduced urinary creatinine excretion in relation to their height, leading to a low creatinine-height index, whereas marasmic children may have a normal or somewhat low index.

Plasma levels of other nutrients vary and tend to be moderately low. They do not necessarily reflect the body stores. For example, serum iron and retinol levels may be normal with almost depleted body stores, or in kwashiorkor they may be relatively low with adequate stores because of alterations in the transport proteins, transferrin, and retinol-binding protein.

Histopathologic Findings. Histopathologic studies show nonspecific atrophy, mainly in tissues with greater cell turnover rates, e.g., intestinal mucosa, red bone marrow, and testicular epithelium; intestinal villi are flattened, and enterocytes lose their columnar appearance. Marasmus is associated with generalized atrophy of skeletal muscle. The skin changes consist of dermal atrophy, ecchymosis, ulcerations, and hyperkeratotic desquamation, seen primarily in areas subjected to irritation and not necessarily restricted to exposed areas, as in the case of pellagra. The liver in patients with kwashiorkor is enlarged, with fatty infiltration; periportal fat appears first and advances centripetally as severity increases. Special staining techniques and electron microscopy reveal generalized tissue atrophy and other alterations that are not specific to primary PEM. Lesions due to superimposed infections and other nutrient deficiencies often are evident macroscopically and on histopathologic examination. These changes usually revert to normal with nutritional recovery, although some residual lesions may persist for some time.

PROGNOSIS AND RISK OF MORTALITY. Weight for height can be restored with adequate treatment, but children's catch-up growth in height may take a long time or might never be achieved. These children have been deprived not only of food but also of opportunities for development, and they may have missed the critical periods for harmonic physical, mental, and social maturation. Many severely malnourished children appear to have residual behavioral and mental problems in terms of creativity, learning ability, and social interaction. This can be partially a result of a poor living environment, however, and the damage may be corrected with adequate care and stimulation.

Mortality rates among children with severe PEM are associated with the quality of treatment. Worldwide, median case fatality has remained unchanged at 20 to 30% for the past 50 years, with levels as high as 40 to 60% among those with edematous PEM as a result of outmoded and faulty management. Low mortality is attainable with adequate treatment, and in some centers it is as low as 4 to 6% for both edematous and nonedematous forms. Table 130–3 lists the characteristics that generally indicate a poor prognosis and demand close surveillance.

TREATMENT

Severe PEM. Whenever possible, patients with uncomplicated PEM should be treated outside the hospital to avoid

TABLE 130–3. Characteristics That Indicate Poor Prognosis in Patients With PEM

- Age <6 months
- Deficit in weight for height >30%, or in weight for age >40%
- Signs of circulatory collapse: cold hands and feet, weak radial pulse, diminished consciousness
- Stupor, coma, or other alterations in awareness
- Infections, particularly bronchopneumonia or measles
- Petechiae or hemorrhagic tendencies (purpura is usually associated with septicemia or a viral infection)
- Dehydration and electrolyte disturbances, particularly hypokalemia, hypernatremia, and severe acidosis
- Persistent tachycardia, signs of heart failure or respiratory difficulty
- Total serum proteins <30 g/L
- Severe anemia (<4gHb/dL) or clinical signs of hypoxia
- Clinical jaundice or elevated serum bilirubin level
- Extensive exudative or exfoliative cutaneous lesions or deep decubitus ulcerations
- Hypoglycemia
- Hypothermia

From Torun B, Chew F: Protein-energy malnutrition. *In* Shils ME, Olson JA, Shike M (eds): Modern Nutrition in Health and Disease, 8th ed. Philadelphia, Lea & Febiger, 1994, p 966.

the risk of cross infections and of increased apathy and anorexia in children due to the unfamiliar setting. Severely malnourished patients with signs of a poor prognosis (Table 130–3) or other life-threatening complications and those who live under deplorable social conditions that do not permit adequate medical and nutritional treatment as outpatients must be hospitalized. Treatment of all forms of severe PEM is similar and consists of (1) resolving life-threatening conditions, (2) initial dietary treatment without disrupting homeostasis, and (3) ensuring full rehabilitation.

Resolving Life-threatening Conditions

FLUID AND ELECTROLYTE DISTURBANCES. Useful indicators of dehydration in severe PEM include a history of watery diarrhea or vomiting, thirst, low urinary output, weak and rapid pulse, low blood pressure, cool and moist extremities, and a declining state of consciousness. Sunken eyeballs and decreased skin turgor are frequently found in well-hydrated patients, whereas hypovolemia may coexist with subcutaneous edema. Treatment differs from that of well-nourished patients, because patients with severe PEM usually have hypo-osmolality with moderate hyponatremia; mild to moderate metabolic acidosis, which disappears when patients receive energy (calories) with the diet and oral or intravenous rehydration solutions; high tolerance to hypocalcemia; decreased body potassium without hypokalemia; and decreased body magnesium, with or without hypomagnesemia.

Whenever possible, oral or nasogastric rehydration should be used. Many clinicians report good results with the oral rehydration salts (ORS) promoted by WHO for children who are not severely malnourished (Chapter 16). Recent WHO recommendations for the management of severe malnutrition advocate the use of solutions that provide more potassium, magnesium, and, especially for edematous PEM, less sodium (30 to 60 instead of 90 mmol/L). A practical approach is the preparation of a mineral mix to complement the diet; this can be combined with WHO's regular ORS and sucrose to prepare a modified ORS solution for patients with severe PEM. Table 130–4 shows the composition of the mineral mix, and Table 130–5 shows the composition of the modified ORS prepared by diluting one standard WHO ORS packet, two 3.12-g packets of mineral mix (*or* 40 mL of concentrated mineral mix solution), and 50 g of sucrose in 2 L of water.

ORS solution should be given at a slower rate than for better-nourished children: 70 to 100 mL/kg body weight over a period of 12 hours, starting with about 10 mL/kg/hr during the first 2 hours for children with mild to moderate dehydration and up to 30 mL/kg/hr for severe dehydration. An additional 50 to 100 mL ORS solution should be given after each loose stool to children <2 years old, and twice as much to older children. Breast-feeding must continue approximately every half hour. Patients must be evaluated every hour. When patients improve, usually 4 to 6 hours after beginning rehydration, small amounts of liquid dietary formula with potassium, calcium, magnesium, and other electrolytes should be offered every 2 to 3 hours. If signs of dehydration are still present after 12 hours but the condition is improving, another 70 to 100 mL ORS/kg can be given over the next 12 hours. Fluid repletion should allow a diuresis of at least 200 mL in 24 hours in children and 500 mL in adults, or micturition every 2 to 3 hours. When signs of overhydration occur, e.g., when the eyelids become puffy, edema increases, the jugular veins become full, or respiratory rate increases, only breast milk or liquid diet should be given instead of ORS.

Children who vomit frequently or cannot be fed orally must be rehydrated by nasogastric tube, giving ORS solution 3 to 4 mL/kg slowly or drop by drop every half hour. If vomiting persists or abdominal distention increases, ORS should be given at a slower rate. If hydration does not improve after 4 hours, intravenous solutions must be started. When vomiting ceases and hydration improves, ORS should be given by mouth. The nasogastric tube can be removed when the patient tolerates oral solutions for 2 hours.

Intravenous fluids must be used for patients with repeated vomiting or persistent abdominal distention and in severe dehydration with hypovolemia and impending shock. Hypo-osmolar solutions (200 to 280 mOsm/L) must be used. Potassium (when urinating) and sodium should not exceed 6 and 3 mmol/kg/day, respectively, and glucose must provide at least 63 to 126 KJ (15 to 30 kcal)/kg/day. Solutions that have been successfully used include a 1:1 mixture of 10% dextrose in water (D/W) either with isotonic saline (i.e., 5% glucose in 0.5 N saline) or with Darrow's solution; a 1:2:3 mixture of 0.17 sodium lactate-isotonic saline-10% D/W; or Hartmann's solution (lactated Ringer's solution). One of these should be infused during the first hour at a rate of 10 to 30 mL/kg, depending on the patient's condition. After that, 5% glucose in 0.2 N saline (800 mL of 5% D/W, 20 mL of 50% D/W, and 200 mL of isotonic saline), or a 1:2:6 mixture of lactate-isotonic saline-5% glucose, with 50 mL of 50% D/W added

TABLE 130–4. Mineral Mix for Preparation of Modified Oral Rehydration Salt (ORS) Solution and to Complement Liquid Foods

Salt	Amount (g)	mmol* in 1 g	mmol in 3.71 g
Potassium chloride	89.5	6.47 K	24 K
Tripotassium citrate	32.4	1.62 K	6 K
Magnesium chloride · $6H_2O$	30.5	0.81 Mg^{+2}	3 Mg
Zinc acetate · $2H_2O$	3.3	0.081 Zn^{+2}	0.300 Zn
Copper sulfate · $7H_2O$	0.56	0.011 Cu^{+2}	0.040 Cu
Total	156.26†		

*1 mmol K = 39.1 mg; 1 mmol Mg = 24.3 mg; 1 mmol Zn = 65.4 mg; 1 mmol Cu = 63.5 mg.

†Divide the 156.26 g into 50 packets with 3.12 g of dry mineral mix, or dissolve 156.26 g in 1 L of water to prepare a concentrated mineral mix solution that can be stored at room temperature. Add one packet or 20 mL of the concentrated solution to each liter of modified ORS solution or of liquid food.

Based on suggestions in Briend A, Golden MHN: Treatment of severe child malnutrition in refugee camps. Eur J Clin Nutr 47:750, 1993.

TABLE 130–5. Composition of *Modified* Oral Rehydration Solution for Severely Malnourished Patients*

Component	Concentration (mmol/Lt)
Glucose	125
Sodium	45
Potassium	40
Chloride	76
Citrate	7
Magnesium	3
Zinc	0.3
Copper	0.04
Osmolarity	300

*Prepared by diluting *one* standard WHO ORS packet, *two* 3.12-g packets of mineral mix (described in Table 130–4), and *50 g* sucrose in 2 L of water, as suggested in Briend A, Golden MHN: Treatment of severe child malnutrition in refugee camps. Eur J Clin Nutr 47:750, 1993.

†1 mmol glucose = 180 mg; 1 mmol Na = 23.0 mg; 1 mmol K = 39.1 mg; 1 mmol Cl = 35.5 mg; 1 mmol citrate = 207.1 mg; 1 mmol Mg = 24.3 mg; 1 mmol Zn = 65.4 mg; 1 mmol Cu = 63.5 mg.

to each 500 mL, should be infused at a rate of 5 to 10 mL/kg/hr, based on hourly evaluations of the patient, until oral therapy is initiated. When the patient is urinating, 2 g KCl (27 mmol K) is added to each liter of the infusion solution.

Patients with severe hypoproteinemia (<30 g/L), anuria, and signs of hypovolemia or impending circulatory collapse should be given plasma 10 mL/kg in 1 to 2 hours, followed by 20 mL/kg/hr of a mixture of two parts of 5% dextrose and one part of isotonic saline for 1 or 2 hours. This increases plasma protein concentration by about 5 to 10 g/L and helps prevent the rapid exit of water from the intravascular compartment. If diuresis does not improve, the dose of plasma can be repeated 2 hours later. Further treatment is similar to that of well-nourished patients. Unless the patient is at risk of imminent death, only plasma tested to be negative for human immunodeficiency virus (HIV), hepatitis B (HBV) and C (HCV) should be used.

Increases in pulse and respiratory rate with weight loss, low urine output, and continuing losses from diarrhea and vomiting suggest insufficient fluid therapy. Increases in pulse and respiratory rate with weight gain after accounting for weight of excreta, pulmonary rales, and appearance or exacerbation of edema indicate overhydration.

Hypocalcemia may occur secondary to magnesium deficiency. When a patient has symptoms of hypocalcemia and serum magnesium determinations are not available, it is essential to give not only Ca but also Mg IV or IM. When the symptoms of hypocalcemia disappear, calcium infusion may be discontinued. IM or PO Mg should follow the initial parenteral dosage. As a general therapeutic guideline, a 50% solution of magnesium sulfate can be given in doses of 0.5, 1, and 1.5 mL for patients who weigh <7, 7 to 10, and >10 kg, respectively. The dose can be repeated every 12 hours until there is no recurrence of the hypocalcemic symptoms or until laboratory analysis indicates maintenance of normal serum Mg concentration. Oral Mg supplementation can then continue at a dose of 0.25 to 0.5 mmol (0.5 to 1 mEq)/kg/day.

INFECTIONS. Infections are frequently the immediate cause of death in severe PEM (Chapter 133.1). Clinical manifestations may be mild, and the classic signs of fever, tachycardia, and leukocytosis may be absent. Antigen-antibody reactions are often impaired, and skin tests e.g., tuberculin, often give falsely negative results. Thus, when patients cannot be closely monitored by experienced personnel, it is safer to assume that all ill and severely malnourished patients have a bacterial infection and to treat them immediately with antibiotics, even before obtaining the results of microbiologic cultures, to cover both gram-positive and gram-negative microorganisms; the latter are particularly common in PEM. The choice of drug varies with the suspected etiologic agent, the severity of the disease, and the pattern of drug resistance in the area. When septicemia is suspected, a broad-spectrum antibiotic or a combination e.g., ampicillin and gentamicin is usually given IV. Other supportive treatment may also be necessary, e.g., treatment for respiratory distress, hypothermia, and hypoglycemia.

Drug metabolism may be altered and detoxification mechanisms may be compromised in severe PEM. To decrease the risks of potential toxicity, including the possibility of absorbing drugs normally not absorbed by a healthy intestine, treatment for intestinal parasites, which is rarely urgent, should be deferred until nutritional rehabilitation is under way.

Because of the high mortality rates associated with measles in severe PEM, patients should be vaccinated on the first day (Chapter 25.1). Because seroconversion may be impaired at this early stage of treatment, a second dose of vaccine should be given before discharge.

HEMODYNAMIC ALTERATIONS. Cardiac failure leading to pulmonary edema and frequent secondary pulmonary infection may develop when there is severe anemia, during or after administration of IV fluids, or shortly after the introduction of high-protein and high-energy feedings or of a diet with high sodium content. Diuretics should be given (e.g., furosemide 10 mg IV or IM, repeated as necessary), and other supportive measures should be taken. Many clinicians advocate the use of digoxin (0.03 mg/kg IV every 6 to 8 hours). *The use of diuretics merely to accelerate the disappearance of edema in kwashiorkor is contraindicated.*

SEVERE ANEMIA. Routine use of blood transfusions endangers patients. Hemoglobin levels improve with proper dietary treatment supplemented with hematinics (Chapter 6). Therefore, blood transfusions should be given only in cases of severe anemia with either <40 g hemoglobin/L, <12% packed cell volume (hematocrit), or clinical signs of hypoxia or impending cardiac failure. When there are no resources for screening the blood supply for HIV, HBV, or HCV, transfusion should be used only in life-threatening situations. Whole blood (10 mL/kg) can be used in marasmic patients, but it is better to use packed red blood cells (6 mL/kg) in edematous PEM. The transfusion should be given slowly, over 2 to 3 hours, and repeated if necessary after 12 to 24 hours. If there are signs of heart failure, 2.5 mL blood/kg should be withdrawn before the transfusion is started and at hourly intervals, so that the total volume of blood transfused equals the volume of anemic blood removed.

HYPOTHERMIA AND HYPOGLYCEMIA. Asymptomatic hypoglycemia can be prevented and treated by feeding small volumes of glucose- or sucrose-containing diets and solutions every 2 to 3 hours, day and night. Severe symptomatic hypoglycemia must be treated intravenously with 10 to 20 mL of 20% glucose solution followed by oral or nasogastric administration of 25 to 50 mL of 10% glucose solution at 2-hour intervals for 24 to 48 hours.

Body temperature usually rises in hypothermic patients given frequent feedings of glucose-containing diets or solutions. Patients must be closely monitored when external heat sources e.g., heavy clothing, heat lamps, and radiators are used to reduce the loss of body heat, because they may rapidly become hyperthermic. It is best to keep patients seminude in an ambient temperature of 30 to 33°C.

SEVERE VITAMIN A DEFICIENCY. A large dose of vitamin A should be given on admission, because severe PEM is often associated with vitamin A deficiency, and ocular lesions can develop as a result of increased demands for retinol when adequate protein and energy feeding begins (Chapter 131.1). Water-miscible retinol should be given PO or IM on the first day at a dose of 52 to 105 μmol (15,000 to 30,000 μg or 50,000 to 100,000 IU) for infants and preschool children, or 105 to 210 μmol (30,000 to 60,000 μg or 100,000 to 200,000 IU) for older children and adults, followed by 5.2 μmol (1500 μg or 5000 IU) PO each day for the duration of treatment. The initial dose should be repeated for 2 more days in symptomatic patients. Corneal ulcerations should be treated with ophthalmic drops of 1% atropine solution and antibiotic ointments or drops until the ulcerations heal.

Initial Dietary Treatment. As soon as the measures to manage the life-threatening conditions have been established, nutritional treatment must begin. This must be gradual and at a relatively slow pace, to avoid deleterious metabolic disruptions. The diet must initially provide energy (calories) and protein in amounts below or near daily maintenance requirements for 2 days, followed by gradual increments every 2 or 3 days, as described later. It is best to begin with a liquid formula fed orally or by nasogastric tube, divided equally into 6 to 12 feedings per day, depending on the

patient's age and general condition. This frequent feeding of small volumes must be given around the clock to avoid fasting for more than 4 hours and to prevent vomiting, hypoglycemia, and hypothermia. For older children and adults with good appetites, the liquid formula can be partly substituted with solid foods that have a high concentration of good-quality, easily digestible nutrients. Intravenous alimentation is rarely justified in primary PEM and can increase mortality rates.

The same diet can be used to treat marasmic and edematous patients, although marasmic patients may require larger amounts of dietary energy after 1 or 2 weeks of dietary treatment. This can be provided by adding more oil or fat to the diet. Diets with as much as 60 to 75% of their energy from fats are usually well tolerated, even if they cause some degree of steatorrhea.

The protein source must be of high biologic value and easily digested. Cow's milk usually is well tolerated and assimilated by severely malnourished children, as are goat's, ewe's, buffalo's, and camel's milk. Human, mare's, and ass's milk, however, have low protein concentrations. Dried skimmed cow's milk has very low energy density, which must be restored by adding sugar and/or vegetable oil. The latter also provides essential fatty acids. Eggs, meat, fish, soy isolates, and some vegetable protein mixtures are also sources of good protein. Most vegetable mixtures have protein digestibility 10 to 20% lower than animal proteins, making it necessary to feed larger amounts. Their bulk might pose a problem in feeding small children.

The diet must be supplemented to provide daily about 5 to 8 mmol K and 0.5 to 1 mmol Mg (1 to 2 mEq)/kg of body weight, and 150 to 300 μmol Zn and 40 to 50 μmol Cu. Sodium content should be low, especially for patients with edematous PEM. This can be accomplished by adding to the diet appropriate amounts of a mineral mix, e.g., that shown in Table 130–4. Additional supplements should include daily doses of 5.2 μmol (1500 μg or 5000 IU) vitamin A, 1.2 mmol (0.3 mg) folic acid, and other vitamins and trace elements in the doses provided by most commercial preparations; these should be higher than the daily recommended allowances for well-nourished persons. Supplemental calcium to provide about 15 mmol (600 mg) daily should be given when nondairy diets are used. Administration of supplemental iron (1 to 2.1 mmol or 60 to 120 mg daily) should begin 1 week after starting dietary therapy. Earlier administration of iron will not elicit a hematologic response (Fig. 130–1), it might facilitate bacterial growth in the organism, and it might produce metabolic disturbances, according to the free-radical theory.

A practical dietary regimen that avoids the danger of initial excessive intakes of protein and energy by hungry patients is based on the preparation of a basic liquid food with high protein concentration and high energy density, as in the examples shown in Table 130–6. Delivery of proteins and energy is gradually increased using different concentrations of the basic food, as shown for infants and preschool children in Table 130–7. The addition of sugar compensates for the dilution of dietary energy. Vegetable oil is added at 5- to 7-day intervals to the diet of marasmic patients who are not gaining weight at an adequate rate (an average of at least 5 g/kg/day) by the second week. The liquid preparations must be limited in the first week to 100 mL/kg/day, offering additional water during or between feedings in order to provide at least 1 mL of total fluids per kilocalorie in the daily diet. After day 8, patients can be fed to satiety (ad libitum).

Another option, which is particularly useful for conditions of relief, consists of preparing a liquid formula from an industrially prepared food, usually based on cow's milk,

TABLE 130–6. Examples of High-Protein, High-Energy Liquid Foods that Provide 3 to 4 g Protein and 135 to 145 kcal/100 mL

Food Used as Protein Source	Amount (g or mL)	Cereal flour or sugar (g)*	Sugar (g)	Oil (mL)†	Water (mL)
Cow's milk, dried, whole	130	50	50	40	1000
Cow's milk, dried, skim	100	50	50	70	1000
Cow's, goat's, or camel's milk, fluid	1000	50	50	40	—
Buffalo's or ewe's (sheep's) milk, fluid	650	50	50	40	350
Yogurt (from cow's or goat's milk, whole)	1000	50	50	40	—
Eggs, soft- or hard-boiled, liquefied	300‡	—	200	60	750
Vegetable mix, flour§	140	—	100	55	1000
Commercial soy protein formulas, powder	250	—	—	10	1000

*First choice: precooked rice, corn, or other cereal flour or heat-popped ground rice. If not available, substitute with either 50 g sugar or 20 mL vegetable oil; this will diminish total protein concentration by about 0.5 g/100 mL.

†When cereal flour is used, one half the vegetable oil can be substituted with isoenergetic amounts of sugar, where 1 mL oil = 2.2 g sugar.

‡About 6 medium-sized chicken eggs.

§High-protein quality mix, such as Incaparina (developed by INCAP: 58% corn flour + 38% cottonseed flour + 4% mixture of vitamins, minerals, and lysine), which provides 1360 kJ (325 kcal) and 27.5 g protein per 100 g of dry flour.

cereal flour, sugar, oil, vitamins, and minerals, which initially provides about 1 g protein and 75 kcal (315 KJ)/100 mL. One week later, a more concentrated formulation is used to provide 2 to 2.5 g protein and 100 to 120 kcal (420 to 500 KJ). Tables 130–8 and 130–9 show options for preparation of equivalent formulas with locally available ingredients. Volumes are limited initially to 100 to 120 mL/kg/day for young children and gradually fed to satiety (ad libitum) when steady weight gain is established. Additional water is offered between feedings.

The liquid diets described for infants and young children can be given to older children and adults, especially to weak, anorexic, and elderly patients. However, adolescents and adults are often reluctant to eat anything other than habitual foods, and liquid diets must be prescribed as a medicine rather than as a food. When appetite improves, a diet based on nutritious traditional foods should be given but with added sugar and oil to increase energy density, plus vitamins and minerals; the liquid diet should be given between meals and at night. A wide variety of foods should be provided in amounts to satisfy appetite, taking into account the patient's inclinations and taboos.

Treatment must initially satisfy average energy and protein requirements, adjusted for age and sex (about 45 kcal and 0.75 g protein/kg/day for adolescents, and 35 to 40 kcal and 0.6 g protein/kg/day for adults), followed by a gradual increase to about 1.5 times the energy and 3 to 4 times the protein requirements by the seventh day. Minerals and vitamins must be provided in amounts at least twice greater

TABLE 130–7. Example of a Dietary Therapeutic Regimen for Children (based on gradually decreasing dilutions of the high-protein, high-energy liquid foods shown in Table 130–6*)

Days from Beginning of Treatment	Proportions of Foods Shown in Table 130–6 + Water		Additional Sugar (g/100 mL)	Additional Oil (mL/100 mL)	Food Volume per Meal (mL/kg/meal)		100 mL Provides	
	Proportions	*Volume (mL)*			*Every 2 hr*	*Every 3 hr*	*Protein (g)*	*Energy (kcal)*
1–2	1 + 2	33 + 67	10	—	8.3	12.5	1–1.3	75–85
3–4	1 + 1	50 + 50	10	—	8.3	12.5	1.5–2	105–115
5–6	3 + 1	75 + 25	5	—	8.3	12.5	2.3–3	120–130
7–8	Undiluted	100 + 0	—	—	8.3	12.5	3–4	135–145
For Marasmic Patients Without Adequate Weight Gain†								
13–17	Undiluted	100 + 0	—	2.5	ad libitum		3–4	160–170
18–22	Undiluted	100 + 0	—	5	ad libitum		3–4	185–195
23–27	Undiluted	100 + 0	—	7.5	ad libitum		3–4	210–220
28–32, etc.	Undiluted	100 + 0	—	10, etc.	ad libitum		3–4	235, etc.

*Formulas should initially be fed at a volume of 100 mL/kg/day. They must be supplemented by appropriate amounts of vitamins, minerals, and electrolytes or by adding to each liter of diet 20 mL (or one packet) of the mineral mix in Table 130–4 and a vitamin mix. After 8 days, the undiluted formula can be fed to satiety (ad libitum). Additional water must be given after or between feedings, to provide each day at least 1 mL of total fluids/kcal in the diet.

†Marasmic patients may require more dietary energy when weight gain is <5 g/kg/day. Half a teaspoonful (2.5 mL) of vegetable oil should be added for every 100 mL of liquid diet at 5-day intervals.

than the recommended daily allowances, following the same schedule as for young children. Except for pregnant women, a single dose of 210 μmol (60,000 μg or 200,000 IU) retinol should be given.

The attitude of the person who feeds the patient is important in overcoming the lack of appetite. Patience and loving care are needed to gently coax a child to eat all the diet. The appearance, color, and flavor of the foods also have a role in appetite and food acceptance. An adequate response to the diet results in disappearance of clinical signs of severe PEM accompanied or followed by weight gain, which in children can be at a rate 8 to 15 (or as high as 25) times that of a normal child of the same age. Some patients show only a fourfold or fivefold increase in catch-up. This is most often associated with insufficient energy intakes (e.g., because of inadequately prepared formula, insufficient amounts of formula given at each feeding, too few feedings per day, anorexia, or lack of patience shown by the person who feeds the child) or with overt or asymptomatic infections; urinary infections and tuberculosis are the most commonly seen asymptomatic diseases.

Ensuring Full Rehabilitation. This last stage of treatment begins when a patient is without serious complications, eating satisfactorily and gaining weight, usually 2 to 3 weeks after admission. It may start in the hospital and continue on an outpatient basis, preferably at a nutrition rehabilitation center or similar facility that gives daytime care. When there is no such facility, the hospital must continue to provide care until a patient is ready for discharge. The importance of continuing the high-energy, high-protein diet until full recov-

TABLE 130–8. Examples of Formulas to Prepare 1 L of a Liquid Food to Provide Around 75 kcal and 1.3 g Protein/100 mL During the First Week of Initial Dietary Treatment

Food Used as Protein Source	Amount (g or mL)	Cereal Flour (e.g., rice, corn) g*	Sugar (g)	Oil (mL)	Water (mL)	Mineral Mix (mL)†	Vitamin Mix (mg)‡
Cow's milk, dried, whole	35	50	50	20	1000	20	150
Cow's milk, dried, skim§	25	50	50	30	1000	20	150
Cow's, goat's, or camel's milk, fluid	250	50	50	20	750	20	150
Buffalo's or ewe's (sheep's) milk, fluid	175	50	50	20	825	20	150
Yogurt (from cow's or goat's milk, whole)	275	50	50	20	725	20	150
Eggs, soft- or hard-boiled, liquefied	100‖	—	100	20	950	20	150
Vegetable mix, flour¶	50	—	100	20	1000	20	150
Commercial soy protein formulas, powder	85	—	50	10	1000	20	150

*If precooked flour and heat-popped ground rice are not available, add 50% more of the food protein source (for example, 52 g instead of 35 g of whole dried milk) plus an additional 25 g sugar *or* 10 mL vegetable oil; when more fluid milk or yogurt is used, the volume of additional water must be reduced by the same amount to make a total volume of 1000 mL.

†See Table 130–4.

‡Can be substituted for with a commercial multivitamin product at the dosage recommended by the manufacturer.

§Similar to the F-75 formula in WHO *Manual for the Management of Severe Malnutrition.* Geneva, World Health Organization. In press.

‖About 2 medium-sized chicken eggs.

¶High-protein quality mix, such as Incaparina (developed by INCAP: 58% corn flour + 38% cottonseed flour + 4% mixture of vitamins, minerals, and lysine), which provides 1360 kJ (325 kcal) and 27.5 g protein per 100 g of dry flour.

TABLE 130–9. Examples of Formulas to Prepare 1 L of a Liquid Food to Provide Around 100 kcal and 2.8 g Protein/100 mL After the First Week of Dietary Treatment

Food Used as Protein Source	Amount (g or mL)	Cereal Flour (e.g., rice, corn) g*	Sugar (g)	Oil (mL)	Water (mL)	Mineral Mix (mL)†	Vitamin Mix (mg‡
Cow's milk, dried, whole	90	50	50	20	20	150	1000
Cow's milk, dried, skim§	70	50	50	40	20	150	1000
Cow's, goat's, or camel's milk, fluid	700	50	50	20	20	150	300
Buffalo's or ewe's (sheep's) milk, fluid	450	50	50	20	20	150	550
Yogurt (from cow's or goat's milk, whole)	800	50	50	15	20	150	200
Eggs, soft- or hard-boiled, liquefied	250‖	—	100	25	20	150	800
Vegetable mix, flour¶	100	—	100	30	20	150	1000
Commercial soy protein formulas, powder	190	—	—	—	20	150	1000

*If precooked flour and heat-popped ground rice are not available, add 20% more of the food protein source (for example, 108 g instead of 90 g of whole dried milk) plus an additional 25 g sugar *or* 10 mL vegetable oil; when more fluid milk or yogurt is used, the volume of additional water must be reduced by the same amount to make a total volume of 1000 mL.

†See Table 130–4. All formulas satisfy calcium requirements, except for the egg-based preparations.

‡Can be substituted with a commercial multivitamin product at the dosage recommended by the manufacturer.

§Similar to the F-100 formula in WHO *Manual for the Management of Severe Malnutrition*. Geneva, World Health Organization. In press.

‖About 5 medium-sized chicken eggs.

¶High-protein quality mix, such as Incaparina (developed by INCAP: 58% corn flour + 38% cottonseed flour + 4% mixture of vitamins, minerals, and lysine), which provides 1360 kJ (325 kcal) and 27.5 g protein/100 g dry flour.

ery has taken place must be clearly explained to the child's mother or caretaker. If this can be done at home, the patient can continue treatment there with regular follow-up in a nutrition clinic or its equivalent or with home visits by trained personnel.

INTRODUCTION OF TRADITIONAL FOODS. When edema has disappeared, the skin lesions are notably improved, patients become active and interact with the environment, appetite is restored, and adequate rates of catch-up growth have been achieved, other foods, especially those available at home, are gradually introduced into the diet in addition to the high-energy, high-protein formula. For children, a daily minimum intake of 3 to 4 g of protein and 500 to 625 KJ (120 to 150 kcal)/kg of body weight (or more in marasmus) must be ensured. To achieve this, the energy density of solid foods must be increased with oil, and protein concentration and quality must be high, using animal proteins, soybean protein preparations, and appropriate vegetable protein mixtures. For example, (1) one part of a dry pulse or its flour (e.g., black beans, soybeans, kidney beans, cowpeas) may be combined with three parts of a dry cereal or flour (e.g., corn, rice, wheat); fat or oil should be added to the mashed or strained pulse during or after cooking in amounts equal to the weight of the dry pulse or flour, and to the cereal preparations in amounts of 10 to 30 mL oil per 100 g dry cereal product, depending on the type of preparation. (2) Four parts of dry rice may be combined with one part of fresh or dry fish; fat or oil should be added in amounts equal to 20 to 40% of the dry weights. The food can be served as separate dishes, or the parts can be mashed or blended and fed as paps to infants and young children. The diet must be supplemented with minerals and vitamins as described for the initial dietary treatment until full nutritional rehabilitation is achieved.

EMOTIONAL AND PHYSICAL STIMULATION. Malnourished children need affection and tender care from the beginning of treatment. This requires patience and understanding by the hospital staff and the relatives. Involvement of parents or relatives must be encouraged. Hospital wards should be brightly colored and cheerful, preferably with music. As soon as children can move without assistance and are willing to interact with the staff and other children, they must be encouraged to explore, to play, and to participate in activities that involve body movements. Relatively small increments in physical activity through active play during the course of nutritional rehabilitation result in faster linear (height) growth and accretion of lean body tissues. Parents should be encouraged to stimulate and teach their children by playing and talking. Toys and play materials can often be made from discarded local articles.

Adult patients should exercise regularly, with gradual increments in cardiorespiratory workload.

TREATMENT OF DIARRHEA AND OTHER HEALTH PROBLEMS. Mild diarrhea often disappears without specific treatment as nutritional status improves. However, persistent or recurrent diarrhea can contribute to the development of a new episode of PEM. Treatment is determined by the underlying cause of diarrhea, usually repeated intestinal infections, excessive bacterial flora in the upper gut that ferment food substrates and deconjugate bile salts, intestinal parasites (particularly giardiasis, cryptosporidiosis, and trichiuriasis), and intolerance to food components (Chapter 133.2). The apparent high prevalence of lactose malabsorption and intolerance in PEM is often founded on inadequate diagnostic procedures. When intolerance to milk or other food is suspected, the diet should be modified, taking care to preserve its nutritional quality and density. Before branding a patient intolerant to a given food, the food should be reintroduced into the diet and adequate diagnostic tests should be performed to confirm the diagnosis.

Other minor complications, e.g., intestinal parasites, must be treated. Children should be vaccinated against infectious diseases.

CRITERIA FOR RECOVERY. Premature termination of treatment increases the risk of a recurrence of malnutrition. The most practical criterion for recovery is catch-up in weight, and almost all fully recovered patients should reach the weight expected for their height or a normal BMI. Repletion of body protein is best assessed through body composition indices,

e.g., the creatinine-height index, which in children requires urine collection for 48 to 72 hours. When body composition cannot be assessed, as a general guideline dietary therapy should continue for 1 month after the patient reaches a normal weight (Tables 130–1 and 130–2) without clinical signs of edematous PEM, or for 15 days after the marasmic patient reaches that weight. Some patients, however, apparently remain underweight because they are in the lower end of the normal distribution curves of weight for height or BMI. If they continue growing at a normal rate and have no functional impairments, treatment can be terminated after 1 month of adequate dietary intake and weight gain (or, in adults, weight stabilization). Specific treatment of other nutritional problems (e.g., iron deficiency) sometimes must be prolonged beyond discharge for PEM.

Before being discharged, patients or their parents must be taught about the causes of PEM, emphasizing rational and nutritious use of household foods, personal and environmental hygiene, appropriate immunizations, and early treatment—including dietary management—of diarrhea and other diseases.

MILD AND MODERATE PEM. Ambulatory treatment must be provided, supplementing the home diet with easily digested foods that contain proteins of high biologic value, a high energy density, and adequate amounts of micronutrients. In some instances, nutritional rehabilitation is achieved merely by instructing mothers in improved child-feeding practices and in more nutritious culinary habits or by instructing adult patients about adequate eating habits and better use of food resources. In most instances, however, it is necessary to provide both nutritious food supplements and instructions for their use.

As a general guideline, patients should have an intake of at least twice the protein and 1.5 times the energy requirements. For preschool children, this would signify a daily intake of about 2 to 2.5 g of high-quality protein and 500 to 625 KJ (120 to 150 kcal)/kg of body weight, and for infants <1 year, about 3.5 g protein and 625 KJ (150 kcal)/kg/day.

This is more likely to be achieved if the diet is appetizing to both the child and the mother, if it is ready made or easy to prepare, if enough is available or provided to feed other children in the same household, and if donated food has no important commercial value outside the home that would make it easy and profitable for the family to sell the item for cash. A substitution effect on the home diet (i.e., a decrease in the usual food intake) is almost always unavoidable, but it can be reduced by using low-bulk supplements with high protein and energy concentrations. Special attention should be given to avoid a decrease in breast-feeding. The supplements for breast-fed infants should be paps or solid foods that do not quench an infant's thirst and thus do not change an infant's demand for nursing or a mother's attitude toward lactation.

Adequate amounts of vitamins and minerals must be provided, although mild deficiencies can be overcome by the micronutrients in the food or by use of fortified vehicles, such as bread enriched with iron or sugar fortified with retinol.

PREVENTION AND CONTROL. Special attention must be given to the availability and rational use of nutritious foods, the control and reduction of infections, and health and nutrition education programs for the individual, the family, and the community. The physician, nutritionist, public health worker, and educator can and must have an active role. However, at a national or regional level, control and prevention of PEM can be achieved only through short- and long-term political commitments and effective actions to eradicate the underlying causes of malnutrition.

When limited resources allow attention to only those more susceptible to PEM, a profile of risk factors is useful. The most likely victims are children <2 years of age and from low socioeconomic strata, whose parents have misconceptions about the use of foods, who come from broken or unstable families, whose families have a high prevalence of alcoholism, who live under poor sanitary conditions in urban slums or in rural areas frequently subject to droughts or floods, and whose societal beliefs prohibit the use of many nutritious foods.

The presence of a malnourished child in a family indicates something amiss in that household and suggests that other members might also be at risk of PEM. Therefore, nutritional and health education must not be restricted to rehabilitation of the index case but should include prevention of nutritional deterioration of other family members, especially siblings and pregnant and lactating women. Similarly, a high prevalence of children with malnutrition or growth retardation indicates that the entire community is at some risk of impaired nutrition. Consequently, education programs must be devised for community leaders, civic action groups, and the community as a whole. Such programs must emphasize promotion of breast-feeding, appropriate use of weaning foods, nutritional alternatives using traditional foods, personal and environmental hygiene, feeding practices during illness and convalescence, and early treatment of diarrhea and other diseases. Personal and communal involvement should be pursued through commitments to apply the recommendations. Toward this aim, it is important that all educational programs incorporate the community's own assessment of their nutritional deficiencies and their feelings toward personal participation in solving these problems.

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131 Vitamin Deficiencies

131.1 Vitamin A Deficiency and Xerophthalmia

Alfred Sommer

DEFINITION. Vitamin A deficiency affects a wide variety of bodily functions. The most obvious and dramatic involve the eye (xerophthalmia). Other, earlier effects include pronounced interference in systemic functions, particularly the ability to contain infectious diseases, especially diarrhea and measles, resulting in increased case severity, morbidity, and mortality. By definition, vitamin A deficiency exists when there is inadequate vitamin A available to target tissues. There are no practical methods to detect directly this deficit, although a variety of surrogates, primarily serum retinol and/or its variants, is an adequate index, particularly on a population level. In general, in the absence of an infectious disease (since acute-phase reactants affect serum levels), retinol levels above 20 μg/dL are considered "normal," although higher levels, 30 μg/dL or greater, are compatible with milder forms of xerophthalmia and systemic consequences (e.g., iron deficiency anemia and childhood mortality).

ETIOLOGY

Sources and Functions. Vitamin A (retinol) is a lipid-soluble essential micronutrient required for a wide variety of important bodily functions. Its most important effects are on cellular differentiation, whether resulting in development of mucous-secreting epithelium (e.g., covering the eye, lining the respiratory and genitourinary tracts) or the immune system. Vitamin A is available from the diet as the preformed vitamin (retinyl ester) or from provitamin A carotenoids (vegetable and plant sources), which are converted in the gut to vitamin A. The vitamin is stored in the liver, which has 90% of the body's stores. It is transported through the blood stream, tightly bound to retinol-binding protein (RBP), to target tissues. Cellular receptors bind the vitamin A–RBP complex, incorporating the retinol into the cell, where it is metabolized to its active form, retinoic acid, which binds to nuclear receptors, regulating gene expression. Another role for vitamin A metabolism is clinically relevant: as an essential component of visual pigments involved in vision, particularly under low levels of illumination.

Risk Factors for Deficiency. Vitamin A deficiency arises primarily from an imbalance between dietary intake and metabolic need. Metabolic needs are increased during growth, infectious diseases, and pregnancy, the latter two helping to explain the higher prevalence of deficiency in developing countries.

The most important determinant is dietary intake, and it is here where differences between developed and developing countries are most apparent. In developed countries, most dietary intake is of the preformed vitamin, either from artificially fortified dietary constituents or from animal food products (e.g., milk and other dairy products, egg yolks, liver and liver oils). By contrast, people in developing countries, particularly children, generally lack access to the preformed vitamin, often receiving vitamin A–depleted skim milk formulas (the nonfortified product loses its lipid-soluble vitamin A when the lipid is skimmed off). Instead, they depend on vegetable sources of provitamin A–rich carotenoids (red palm oil, colored fruits [e.g., mango and papaya], and dark green leafy vegetables). Pure β-carotene is readily converted to vitamin A. Dietary sources, however, bind β-carotene closely, making conversion inefficient. Recent studies in Indonesia and elsewhere suggest that pure dark green leafy vegetables and similar products have a conversion rate of only 5% to 15%, even when cooked and sieved. Given the constraints on busy mothers, the low levels of conversion, and the dislike of dark green, leafy vegetables by young children, it is surprising that vitamin A deficiency is not even more severe and widespread.

Requirements. Vitamin A requirements, largely extrapolated from the needs of healthy adults, are 300 retinol equivalents (RE) daily for infants, and 750 RE for adults. One RE is equivalent to 1 μg of retinol and to 6 μg of β-carotene; however, in most instances the equivalent amount of dietary carotene should be considerably higher. Poor children in developing countries having intestinal parasites and other frequent, chronic, and endemic infections have an increased requirement for vitamin A.

EPIDEMIOLOGY. Clinically significant vitamin A deficiency is only rarely encountered in wealthier, Western countries, where it is largely confined to individuals on highly restricted diets, or with end-stage liver disease or severe malabsorption syndrome (e.g., cystic fibrosis).

The great magnitude of disease occurs among children, and to a lesser degree, pregnant women in poor, often tropical countries. Although the number of children with marginal deficiency is unknown, an estimated 5 to 10 million children develop xerophthalmia, while half a million go blind from the condition every year. One to 3 million children die from the deficiency annually. The problem is sufficiently widespread that over 60 countries recognize the existence of vitamin A deficiency as a public health problem and have launched, or planned, large-scale, population-wide control programs.

Deficiency is most widespread and severe in young children, particularly those who did not benefit from prolonged breast-feeding (the best early dietary source of vitamin A and a practice that reduces the risk of infection). Young children, particularly those between 1 and 4 years of age, are also at increased risk because of their limited dietary choices and high rates of childhood infection. Childhood exanthemous diseases can have a particularly dramatic impact on vitamin A status.

Vitamin A deficiency is characterized by "clustering." Children (and mothers) living in the vicinity of a case of xerophthalmia are far more likely to be deficient than those living in a more distant family or compound. Presumably this reflects communal dietary practices and hygiene, and shared risks of protein malnutrition and infection. As children grow older, their dietary tastes change, they forage more widely, and they are at lower intrinsic risk of infectious morbidity and mortality. Most recognized clinical diseases (and deficiency) exist in south and Southeast Asia (India, Indonesia, Pakistan, Bangladesh, Thailand, Philippines) and most of Africa.

PATHOPHYSIOLOGY

Causes for Deficiency. Prolonged vitamin A intake inadequate to meet bodily demands eventually leads to a decline in liver stores, followed by a fall in serum levels, and finally