



## Chapter 11

# Infections and Immunity

There are sure to be two prescriptions  
diametrically opposite. Stuff a cold and  
starve a cold are but two ways.

Henry David Thoreau  
(1817–1862)

*A Week on the Concord and Merrimack  
Rivers, "Wednesday"*

### Introduction

Interactions among nutrition, infections, and immune disorders have important implications for individual, public, and economic health in this Nation and around the world. In the past decade, substantial advances in scientific knowledge have occurred in the study of malnutrition, the determinants of infection, and the components and functions of the immune system. Nevertheless, many details of this complex three-way interaction remain unclear. This chapter reviews the physiologic and immunologic mechanisms that protect people against illness, nutrition's role in the proper function of these mechanisms, malnutrition's negative effects on immune function, infectious illnesses and their detrimental effects on an individual's reserves, food allergies that cause adverse reactions, and the problems of food-associated illnesses and other diseases.

### Historical Perspective

Famine and pestilence have been closely associated throughout recorded history. Ancient scriptures in India noted the apparent relation of diet and the ability to resist disease (Chandra 1983). Episodes of plagues, for example, have been recorded throughout history, although the influence of malnutrition on these outbreaks is not certain. During wars, dysentery, typhus, and smallpox were leading causes of death; malaria, diarrheal diseases, typhoid, measles, and pneumonia also caused many deaths. Poor nutrition and contaminated food invariably accompanied episodes of infectious disease. Although the impact of malnutrition on such infections is difficult to determine, malnutrition may predispose to or alter the severity of infection, and most infections aggravate malnutrition (Beisel et al. 1977; Alexander and Stinnett 1983).

Modern public health concepts concerning sanitation, water purification, good nutrition, and immunization have helped eliminate many infectious diseases in the United States. By the early 1900's, the importance of adequate nutrition and vitamins was recognized. For many years before specific antimicrobial therapy became available, a combination of bedrest and wholesome foods was commonly used with varying effectiveness to treat subacute and chronic infections such as tuberculosis. The introduction of antibiotics in the 1940's led to the control of many infectious illnesses, especially those caused by bacteria.

Vaccines have now made possible the control or elimination of many infectious diseases. For example, live-virus vaccines against measles, mumps, and rubella, first available in the 1960's, have dramatically improved the control of these diseases. Other once commonplace infections, such as cholera, typhoid fever, tetanus, rabies, poliomyelitis, diphtheria, and pertussis, have been virtually eliminated in the United States or drastically reduced by immunization programs and improved environmental and social conditions (Braude 1985). Smallpox was the first communicable disease to be eradicated worldwide, with the last known indigenous case occurring in October 1977 in Somalia (Chin 1980). Nonetheless, nutritional status can affect the immune response stimulated by vaccination; hence, especially in developing countries, nutritional and vaccination programs are essential components of infectious disease control strategies.

Food-borne microbial illness is a significant issue in infections. Since the 1906 enactment of the Wiley Act, the first pure food and drug law, much legislation has been passed to protect the food supply from infectious micro-organisms. Federal and State governments conduct or promote many activities to prevent food-borne diseases from threatening the Nation's health: they establish safety standards, inspect food establishments serving the public, train food handlers and food sanitarians, certify milk and shellfish shipped interstate, inspect meat and poultry, monitor outbreaks of disease, and act to eliminate the sources of food-borne microbial illness (Hartman, Porter, and Withnell 1981). To minimize or eliminate micro-organisms from the commercial food supply, the food industry uses a variety of processing methods and preservatives. Occasionally, a serious breach of safety in a commercial plant or process has resulted in a serious outbreak of food poisoning.

Today, and in the past, many infections occur with greater severity and some infections occur more frequently in malnourished persons than in well-nourished people. Yet, as will be discussed, many aspects of the relationships of malnutrition to immune responses and to susceptibility to

infection are still poorly understood. Although malnutrition due to prolonged food deprivation may increase the risk for infection, malnutrition is more likely to be a result than a cause of an infectious or other serious disease. During the prolonged starvation suffered by inhabitants of the Jewish ghetto in Warsaw during World War II, for example, almost 500 deaths were attributed solely to simple starvation, but many more deaths occurred because of malnutrition in combination with tuberculosis, typhus, or other infectious diseases. Not surprisingly, most of the population showed clinical evidence of poor immune function (Winick 1979).

Even now, despite many medical advances, the combined effects of infection and malnutrition constitute the most common cause of death among children throughout the developing world (Chen 1983), and they remain as major problems among premature and low birth weight infants—and among severely ill hospitalized patients—in the United States (Chandra 1983; Keusch 1984).

The history of food allergies and intolerances is less well known. Hippocrates (460–370 B.C.) and Galen (131–210 A.D.) reported a relationship between consumption of specific foods and allergic digestive and skin symptoms, specifically describing reactions to ingestion of cow and goat milks, respectively. Systematic observations of food allergies began to appear in the 20th century, and recently, the literature in this field has grown rapidly (AAAI 1984). Diet may also cause disease by transmitting infectious microorganisms or toxic substances that enter or are contained within the natural foods.

### **Significance for Public Health**

Tremendous progress has been made in infectious disease control during the past century, yet, except for smallpox, infectious diseases remain a serious public health problem. In 1982, for example, over 25,500 tuberculosis cases were reported, along with hundreds of thousands of salmonellosis and hepatitis cases and millions of cases of sexually transmitted diseases, hospital-acquired infections, influenza, and other acute respiratory illnesses (CDC 1983). In the past decade, new varieties of infectious disease (e.g., legionnaires' disease, toxic shock syndrome, AIDS, viral diarrheas) have emerged, often with fearsome consequences. The ultimate conquest of infectious diseases, therefore, is far from over.

In the developing world, where food and water supplies are often contaminated with microorganisms, food-borne diseases take their highest toll. In 1980, more than 1 billion cases of diarrheal diseases were estimated to

occur in children under age 5 (Chen 1983). Contaminated food and water were largely responsible for the high rates of infant and childhood mortality recorded among developing populations.

Despite high standards of sanitation in the United States, the incidence and costs of food-associated disease are considerable (although assessments of the magnitude of the problem vary widely due to difficulties with data collection and case reporting). In the United States in 1982, only 656 outbreaks of food-borne disease were reported to the Centers for Disease Control (CDC 1983). However, published estimates range from 24 to 81 million cases per year of gastrointestinal illness due to contaminated food or person-to-person spread (Archer and Kvenberg 1985). In cases in which the causes were confirmed, bacterial pathogens accounted for approximately two-thirds of the outbreaks and chemical agents for about one-fifth. Parasitic and viral outbreaks occur more infrequently in the United States. Although an outbreak is defined as an incident in which two or more persons experience a similar illness after eating a common food or in which epidemiologic analysis implicates food as a source of illness, a single case of botulism or chemical poisoning also constitutes an outbreak (CDC 1985). The discrepancies in estimates are due to limitations in the available data. The economic costs of food-associated illness have been estimated to range from \$1 billion to \$10 billion annually for direct medical costs, lost wages, and reduced industrial productivity (Todd 1984). A more recent analysis has placed the economic costs as high as \$23 billion, excluding costs to industry (Archer and Kvenberg 1985).

Because gastrointestinal, skin, and respiratory symptoms of food allergies and intolerances resemble those caused by many other conditions, the true incidence of these food-related problems has been difficult to establish. Unexplained symptoms are often attributed to food allergies when no other reason can be found or when the symptoms improve after the offending food is removed from the diet. The percent of food allergy cases confirmed in double-blind food challenges is usually quite low. Estimates of the incidence of cow milk allergy have ranged from 0.3 to 7.5 percent, with higher rates reported for infants than for adults. Rates as high as 25 percent have been reported in individuals who had eczema as infants or asthma in childhood. The percentage of the population that reacts adversely to foods or food components is unknown (AAAI 1984).

## Scientific Background

### Effects of Malnutrition

Simply defined, malnutrition means poor nutrition, but malnutrition may take many forms, including excesses as well as deficiencies of body nutrients. Both deficits and excesses may be generalized, involving multiple nutrients, or they may be limited to one, or only a few, of the many nutrients the body needs to maintain normal health and body composition. Most forms of malnutrition appear to make the human body more susceptible to infectious diseases. Obesity has been linked with increased susceptibility to infection only rarely. Malnutrition is a far more common association (Edelman 1981).

Many forms of malnutrition also have detrimental effects on immune system function (Suskind 1977; Stinnett 1983). These adverse influences of malnutrition depend, to a large degree, on the severity of the nutritional deficiency (Scrimshaw and Wray 1980). Most reported examples of the interaction between malnutrition and infection deal with severe generalized malnutrition, which is also called cachexia. Dry (nonedematous) cachexia has also been termed marasmus, whereas wet (edematous) cachexia is known as kwashiorkor. The terms protein-calorie or protein-energy malnutrition are widely used in medical literature to denote generalized undernutrition, but these terms fail to indicate that most clinical forms of generalized malnutrition involves multiple nutrient deficiencies as well as protein and other sources of metabolizable energy. In contrast to severe generalized malnutrition, far less is known about the effect of single nutrient deficiency (e.g., vitamins, minerals, trace elements, amino acids, and unsaturated fatty acids) on the immune system function and other host defensive mechanisms (Beisel et al. 1981; Beisel 1982a; Chandra 1988).

### Effects of Infectious Disease

Infectious agents include a wide variety of micro-organisms such as bacteria, viruses, rickettsia, fungi, and parasites. When an infectious agent invades a host, the results can range from no disease to an acute or chronic illness. Whether a clinically apparent infection develops depends on the virulence (ability to cause serious illness) and dose of the invading micro-organism, the route by which the micro-organism enters the body, and the

host's ability to resist infection. This ability is influenced by age, sex, heredity, previously acquired immunity, the presence or absence of other disease processes, and overall nutritional status. Depending on its severity, generalized or single nutrient malnutrition can adversely affect the structure and function of various body cells and tissues. These deficiencies can secondarily impair the adequacy of many non-specific host defense mechanisms (Suskind 1977). The weakening of immunologic and nonspecific defenses can lead, in turn, to a more severe illness (Scrimshaw et al. 1986). Infectious diseases and immune functions are intimately linked to each other as well as to nutritional status, and each of these variables are interactive (Beisel 1982b, 1984; Chandra 1983). Although each species of virulent bacteria, virus, parasite, or other disease-causing micro-organism produces a different, but characteristic, illness in humans, the nutritional consequences of most acute infectious diseases are quite similar. These consequences occur as a result of fever, loss of appetite, vomiting and diarrhea, and other symptoms of generalized infection. The overall increase in body metabolic rates and the reprioritization of many biochemical pathways during acute infections combine to increase the body's requirements for nutrients as well as simultaneously to increase body losses of nutrients (Beisel 1985). These nutritional costs of infection occur at a time when food intake is reduced by anorexia. Thus, the magnitude of nutrient depletion often depends more on the severity and duration of illness than on the species of infecting organism.

Most infections stimulate protective immune responses; however, some responses are harmful. Examples are kidney inflammation (Bright's disease) or rheumatic fever after some streptococcal infections and heart or thyroid inflammation after certain viral infections. Abnormal function of the immune system increases the chance for infections that lead to malnutrition. As will be discussed later, malnutrition depresses the immune system and makes infected people more susceptible to still other infections (Scrimshaw, Taylor, and Gordon 1968). Malnutrition, depressed immunity, and infection thus interact in a cyclical downhill spiral that can eventually lead to death (Mata 1975; Keusch 1984).

#### Nonspecific Host Defense Mechanisms

Nonspecific defenses include both active and passive components. Passive mechanisms (such as normal microbial flora, skin and mucous membranes, and body surface secretions) help prevent micro-organisms from entering body tissues. For example, surface secretions and coughing cleanse the lungs and prevent microbial entry, as does the production of mucus in the intestine and normal intestinal motion. Many of these passive components are impaired by inflammation and in severely malnourished patients.



The more active forms of nonspecific host defenses include the ability of body cells to kill micro-organisms or to release substances that aid in eliminating them. These defenses are also impaired during malnutrition (Beisel 1985; Kauffman, Jones, and Kluger 1986). For example, whenever an infection begins, acute-phase responses are triggered by the release of interleukin-1 (IL-1) and other substances from body cells (Kluger, Oppenheim, and Powanda 1985; Dinarello 1988; Movat et al. 1987). IL-1 is a hormone-like mediator produced by activated blood monocytes and tissue macrophages. In addition to its ability to stimulate the immune system through its action on lymphocytes, IL-1 initiates numerous metabolic and physiologic changes that make up the nonspecific but active host defense mechanisms known as acute-phase responses. IL-1 acts on the brain (Breder, Dinarello, and Saper 1988) and on the liver, islet of Langerhans cells in the pancreas, bone marrow, contractile cells of skeletal muscle, circulating blood granulocytes, vascular endothelium, intestinal mucosa, and adipocytes of fat depots (Beisel 1985; Dinarello 1988). Another defense mechanism is the complement system, which includes about 20 proteins that circulate in inactive forms in the blood. When an infection occurs, these proteins are activated to produce inflammatory responses, membrane lysis, and other effects that cause bacterial death (Claman 1987). These nonspecific defense responses are also impaired by malnutrition, as will be discussed later in this chapter.

### Cellular and Humoral Immunity

The immune system protects the body against infection by producing specific substances in response to foreign materials called antigens. Immunity to specific antigens occurs through the cooperative interactions of two subsets of blood cells, T lymphocytes and B lymphocytes, that give rise to cell-mediated (cellular) and antibody-mediated (humoral) immunity, respectively (Claman 1987).

Cell-mediated immunity is provided largely by thymus-dependent T lymphocytes. There are several subtypes of T lymphocytes, each with specific functions. Helper and suppressor T lymphocytes regulate the quantities of antibodies produced, while killer T lymphocytes, which respond selectively to foreign material, can search and destroy internally infected, transplanted, or malignant body cells. Each T lymphocyte class responds to different types of infection or to different forms of malnutrition (Beisel 1982a, 1984). Mature lymphocytes in blood can be classified by their function and by unique marker molecules on their surfaces.

Humoral immunity is provided by antibodies, which are specific immunoglobulin (Ig) proteins produced by B lymphocytes in response to specific

antigens. Antibodies of various classes, such as IgM, IgG, or IgA, are of major importance in preventing or terminating infections of many different types, and they also neutralize toxins of bacterial origin, such as those produced by diphtheria or tetanus bacilli (Braude 1985). This protection can be long term. Exposure to a specific antigen, either through an infection or vaccination, stimulates the immune system to produce antibodies.

Preformed, concentrated antibodies against specific antigens and contained in serum (e.g., antiserum or antitoxin) can be administered therapeutically or prophylactically to provide direct immediate short-term passive immune protection. For example, antitoxin is used to treat botulinism, and hyperimmune globulin is given to help prevent hepatitis. In addition to these protective functions, harmful immune responses sometimes can occur as a consequence of circulating antibodies, as in allergies or autoimmune diseases.

#### Methodological Issues

Despite recent advances in immunologic methodology that permit identification of pathogens and various subsets of lymphocytes, clinical assessment of immune function is still quite difficult and uncertain, especially under field conditions. Immunologic responses to antigens may take months to develop. Skin testing for immediate and delayed reactions to antigens is not specific enough to accurately assess infection or immunologic function in all situations (Miller 1978). Adequate methods to evaluate the immunologic status of body surface secretions, especially within the gastrointestinal tract, have not yet been developed. Although the functional capabilities of various types of immune system cells can now be evaluated in specialized laboratories, these studies require exacting techniques to transport the blood sample, to isolate the cells, and to maintain them in culture throughout the testing. As a result of these difficulties, few reliable data have been obtained in human subjects on the influence of individual essential nutrients on specific immune system functions or on the mechanisms of interaction between nutrition and immunity (Chandra 1981; Solomons and Keusch 1981). In addition, as with other studies in diet and health, the use of animal models for the study of infection and malnutrition presents problems. Animal species differ from each other and from humans in their nutritional requirements, rates of growth, and susceptibility to infections (Chandra 1983). The amounts of protein in a diet, for example, and the duration of feeding, the age, and the species of animal studied can all influence immune responses (Jose and Good 1973).



## Key Scientific Issues

- Effects of Malnutrition on the Immune System
- Effects of Infection on Nutritional Status
- Role of Diet-Immune System Relationships in Food-Associated Illnesses

### Effects of Malnutrition on the Immune System

#### Role of Generalized Malnutrition

Throughout the world, generalized malnutrition is a common cause of acquired, correctable immune system dysfunction (Chandra 1983; Suskind 1977; Stinnett 1983). Deficits in both calories and protein tend to be closely linked during generalized malnutrition, and it has not been possible to separate their effects on the immune system. Infectious diseases are extremely prevalent in children with either the marasmus or kwashiorkor forms of generalized malnutrition (Brown et al. 1981). The impact of malnutrition on infectious illnesses is not clearly evident when the malnutrition is mild.

Generalized malnutrition increases both the likelihood of contracting an infectious disease and the severity of infections such as tuberculosis, whooping cough, herpes, bacterial and viral diarrheas, as well as systemic parasitic infections. Severe malnutrition suppresses a person's ability to generate fever, inflammatory responses, or leukocytic reactions (Garre, Boles, and Yovinov 1987). In persons with severe, prolonged diseases, generalized malnutrition increases susceptibility to all infections, but especially those caused by opportunistic organisms that do not usually cause disease in healthy individuals (Baron 1986).

Malnutrition's effects on infection may be synergistic, antagonistic, or show no apparent interaction. In synergistic interactions, infections are made worse by malnutrition, whereas antagonistic interactions occur when an infection is milder than would be expected in a malnourished host. Although most bacterial infections become more severe with malnutrition, nutrient deficiencies have attenuated some viral infections (Scrimshaw, Taylor, and Gordon 1968). The generalized weakening of host defensive mechanisms, including those of the immune system, can explain synergistic interactions. Antagonism occurs because host cells and invading

micro-organisms compete for available nutrients and because host-immune reactions that normally produce disease symptoms are suppressed. Viruses, for example, must use metabolic processes of the host cell to multiply, and nutritionally deprived cells may not contain the nutrients needed for viral proliferation (Beisel 1982b). Parasites such as malaria may also be less able to multiply when the patient is malnourished (Murray and Murray 1977; Solomons and Keusch 1981). Tuberculosis may be acutely exacerbated by feeding starving people; the body's inflammatory reaction to the tuberculous bacillus, which was suppressed by starvation, may flourish after feeding and cause symptoms, particularly if the patient has not received antituberculosis drugs (Murray and Murray 1977).

Malnutrition due to starvation produces different effects on metabolism and body composition than those due to illness or injury, and this difference profoundly affects susceptibility to infection (Beisel 1987). During uncomplicated starvation, extensive metabolic changes serve to conserve body protein stores. Metabolic rate is reduced, nitrogen is conserved, and the use of body fat as a source of energy is increased. Because protein is saved, immune system competence and resistance to infection persist until starvation is greatly advanced (Kerndt et al. 1982).

In contrast, the extreme body wasting (cachexia) caused by acute illness or injury is associated with rapid protein breakdown and a concomitant weakening of resistance mechanisms. Metabolic rate and loss of body nitrogen increase, and large quantities of gluconeogenic amino acids are metabolized to produce glucose; branched chain amino acids are oxidized in muscle cells to produce energy; and the metabolic destruction of tryptophan and phenylalanine is accelerated (Beisel 1985). Such diversions of free amino acids reduce their availability for the synthesis of new proteins. The adequacy of immune functions and other host defense mechanisms ultimately depends on the ability of body cells to synthesize a variety of new proteins. But protein synthesis is impaired when the supply of free amino acids is inadequate or when an imbalance exists among the essential free amino acids. Thus, when overwhelming disease or trauma causes severe generalized malnutrition, the resulting deficits of body protein and free amino acids can be linked directly to a depression in host resistance (Beisel 1985). In short, the metabolic consequences of fever and loss of appetite lead to poor nutritional status, deficits in immune system competence, and an increased susceptibility to infectious disease within a relatively short time period (Beisel 1984).

Severe malnutrition due to any cause will impair cell-mediated immunity and may affect immunity mediated by antibodies circulating in the blood and secreted by mucosal surfaces (Suskind 1977; Chandra 1983; Stinnett 1983; Gershwin, Beach, and Hurley 1985; Watson 1984). Patients with severe generalized malnutrition consistently exhibit atrophy and other defects of the lymphoid tissues of the immune system. The total number of lymphocytes is reduced, with the greatest losses occurring among T lymphocytes (Suskind 1977). These abnormalities lead to poor T cell function, diminished ability to reject grafted tissue, and a reduction in secretion of lymphokines and other anti-infective substances.

Even with severe malnutrition, however, total antibody production remains normal and may even be accelerated if infection is present (Chandra 1983). The capacity to produce or to secrete the immunoglobulin IgA into the fluids that cover mucosal surfaces of the body is diminished, however, and specific antibody responses to new vaccines or other new antigens are clearly depressed despite maintenance of nonspecific blood immunoglobulin levels.

When infections occur in malnourished patients, concentrations of individual components of the complement system tend to decline rather than to show a typical infection-induced increase (Suskind 1977; Keusch and Farthing 1986). Complement system deficiencies depress immune system function (Watson 1984) and increase the risk of bacterial infections (Chandra 1983).

With severe generalized malnutrition, the production and mobilization of phagocytes (the cells of the immune system responsible for ingesting microbes or other cells and foreign materials) are often reduced in number. Phagocytic cell function is also impaired, including their responses to stimuli, their participation in inflammatory processes, and their ability to ingest and kill invading micro-organisms (Beisel 1984; Keusch 1984; Garre, Boles, and Yovinov 1987).

Severe generalized malnutrition impairs tissue integrity and causes damage to epithelial surfaces, loss of respiratory tract cilia, and reduction of mucosal secretions. The bacteria in the intestine may be altered, and the normally sterile upper small bowel may become colonized. The stomach's secretion of hydrochloric acid is reduced (Kerndt et al. 1982). All of these defects in the nonspecific defense mechanisms can increase the risk for infection by pathogenic micro-organisms. Dietary replenishment to correct the identified deficiencies can resolve these problems.

### Role of Specific Dietary Factors in Immunity

Certain nutrients described in the following sections are particularly important to immune system function.

**Protein.** Proteins in food provide the body with essential and nonessential amino acids as well as contribute 4 kcal/g to the body's overall energy needs. An adequate intake of animal protein, or certain mixtures of vegetable proteins in the diet, will yield the balance of free amino acids necessary to allow for an optimal synthesis of new body proteins, including those that maintain immune functions. If dietary protein intake is excessive, the unneeded amino acids are broken down (deaminated), and their carbon skeletons are either diverted into energy generation or stored as fat. On the other hand, a prolonged deficit in protein intake will contribute to generalized undernutrition.

There is a normal continuous turnover of proteins in the body, with both the catabolism and anabolism of individual body proteins taking place concurrently. Anabolic protein synthesis predominates during periods of active body growth and during convalescence from illness if protein intake is adequate. Both the anabolic and catabolic processes are accelerated during acute infectious illnesses, but catabolic activity predominates. The role of protein and amino acid metabolism in body defensive reactions will be described in subsequent portions of this chapter.

**Carbohydrate.** Dietary carbohydrate serves chiefly as a source of metabolic energy for the body. Like excessive dietary protein, excessive carbohydrate in the diet will be diverted into fatty acid molecules and deposited in body fat depots. During infection, most of the extra energy needed to produce hypermetabolism and fever comes from the oxidation of glucose. Various hormonal and metabolic stimuli accelerate the manufacture of new glucose (chiefly within the liver) during infection. If the body is unable to sustain the gluconeogenic process, severe hypoglycemia may occur as a terminal complication of infection. This problem is most likely to develop during neonatal sepsis, gram-negative septicemia, or severe hepatitis.

**Fats.** Dietary fats contribute about 9 kcal/g to body energy needs as their principal metabolic function. In addition, a small quantity of essential unsaturated fatty acids in the diet is required for maintaining the integrity of the exterior surface membrane of body cells and for mounting primary and secondary antibody responses (Chandra 1981). However, a dietary excess of polyunsaturated fatty acids, such as linoleic acid, can suppress cell-mediated immune functions in mice (Mertin and Hunt 1967). The greatest

immune suppression in experimental animals seems to occur when the excess polyunsaturated fatty acids have the highest numbers of unsaturated carbon:carbon bonds per molecule (Beisel 1982a).

Fatty acid-derived mediators of inflammation are important in allergic and other inflammatory diseases. For example, asthma patients were put on diets enriched with high- and low-dose eicosapentaenoic acid (EPA) for 8 weeks (Payan et al. 1986). When leukocytes from study patients were examined, it was found that those taken from patients on the high-dose regimen had inhibition both of white cell migration to sites of inflammation (chemotaxis) and the generation by white cells of potent chemical mediators (leukotrienes) of the inflammatory component of chronic asthma when compared with those on the low-dose regimen. However, the clinical role of EPA is still open to question because EPA at either dose did not affect the clinical course of asthma.

There is little doubt that excess quantities of host lipids, occasioned by high-fat, high-energy diets or by lipid infusions, can initiate changes in immune function. However, solid evidence directly linking obesity, high-fat diets, and hyperlipidemia with the outcome of human infection is meager (Edelman 1981). The incidence of only one category of infections, postoperative wound infections, is clearly increased in obese patients, and the mechanisms of this effect may be other than nutritional. Moreover, there are no convincing data in humans on the interaction of obesity, body lipids, and autoimmune diseases (Edelman 1981).

*Vitamins and Minerals.* As discussed throughout this report, deficiency diseases such as scurvy (from vitamin C deficiency), pellagra (niacin deficiency), beriberi (thiamin deficiency), and anemia (iron deficiency) are often associated with decreased resistance to infection. Of special recent interest, for example, are the findings that adequate vitamin A protects against complications of measles (Anonymous 1987) and is associated with overall improvements in mortality rates (Sommer et al. 1986). Subclinical deficiencies of vitamins and minerals may also affect host defense mechanisms (Beisel et al. 1981; Beisel 1982a; Good, Hanson, and Edelman 1982). The lack of information about threshold values at which a nutritional deficit might impair the immune system, however, makes research in this area difficult.

Deficiencies of zinc, pyridoxine, iron, folate, vitamin B<sub>12</sub>, choline, or methionine have been associated with reduced function of T cells (Good, Hanson, and Edelman 1982; Chandra 1985). Zinc is required for adequate

function of T lymphocytes and cell-mediated immunity in several animal species (Fraker, Caruso, and Kierszenbaum 1982; Beisel 1982a). In humans, persons with acrodermatitis enteropathica, an inherited inability to absorb zinc, have severe immune system failure, widespread infections of skin and mucosa, and early death. When instituted early enough, correction of body zinc deficits in these patients has been followed by functional recovery of the immune system, elimination of infections, and a return to good health (Allen, Kay, and McClain 1981; Castillo-Duran et al. 1987). When volunteers ingested excessive zinc, however, the phagocytic functions of neutrophils and the response of lymphocytes to mitogens were impaired (Chandra 1984).

Deficiencies of ascorbic acid, iron, vitamin B<sub>12</sub>, folate, and zinc all impair neutrophil function, although in different ways (Good, Hanson, and Edelman 1982). Although deficiency of vitamin C blocks the mobility of neutrophils, clinical trials have failed thus far to demonstrate that massive daily doses of vitamin C either prevent or cure the common cold or that it improves immune system functions beyond normal (Beisel 1982a; Gershwin, Beach, and Hurley 1985).

As discussed in the chapter on anemia, iron deficiency has been associated with increased incidence of certain infections (Chandra 1981), perhaps because it impairs the function of peroxidase enzymes and leads to deficits in the production of free oxygen radicals and hydrogen peroxide that can kill ingested bacteria (Beisel 1982a; Stinnett 1983).

#### Age-Related Issues

*Infants.* As discussed in the chapter on maternal and child nutrition, prematurity and low birth weight increase the risk for infectious disease, other complications, and consequent mortality. The fetus receives immunoglobulins from the mother by selective transfer across the placenta, but infants born to undernourished mothers typically have abnormally low antibody concentrations in plasma once autonomous antibody production begins. In developing countries where standards of sanitation are poor and children are exposed to multiple infections, children may in fact demonstrate a precocious rise in antibody concentrations compared with adult values (Chandra 1983). Nevertheless, the infant's immune system can be easily overwhelmed by gastrointestinal infections. Such infections prevent intake, absorption, and utilization of food energy and nutrients and initiate the debilitating cycle of infection, diarrheal disease, malnutrition, and, often, death.

Breastfeeding provides an infant both with nutrients and some degree of immunity against infections (Chandra 1979; Welsh and May 1979). Even under conditions of poor sanitation and poverty, breastfeeding protects an infant and fosters normal growth (Mata 1975). Once an infection is established, breastfeeding provides additional protection against its severity (see, for example, Victora et al. 1987). Such protection has been observed in studies in the United States (Duffy et al. 1986), although its overall clinical significance in industrialized societies is uncertain (Leventhal et al. 1986; Bauchner, Leventhal, and Shapiro 1986). In bottle-fed infants, unsanitary conditions, use of contaminated water in preparing bottles, and the lack of maternal antibodies all contribute to infections, especially diarrheal illnesses (see chapter on maternal and child nutrition).

*Older Persons.* The extensive anatomical and physiologic changes that characterize aging are reviewed in the chapter on aging. One change is a gradual senescence of some—although not all—components of the immune system. Studies in experimental animals and in humans reveal a gradual atrophy of the thymus gland along with decreases in the numbers of T lymphocyte helper/inducer cells and in cell-mediated immune functions (Katz 1982). Such changes are similar to those observed in malnutrition. As discussed in the chapter on aging, distinguishing such age-related physiologic changes from those due to malnutrition in older persons has not yet been possible. Progressive impairment of cellular immunity with age might cause the older population to have more infections than younger people of equivalent nutritional and health status, and if malnutrition is responsible for depressed immune functions, improved diet should restore such functions and improve disease resistance. Research has not yet resolved these issues, and the relationships among malnutrition, infections, and changes in immune system functions in elderly persons have yet to be clarified (Thompson, Robbins, and Cooper 1987).

### **Effects of Infection on Nutritional Status**

As noted earlier, severe infections can compromise nutritional status through a variety of mechanisms: hypermetabolism, appetite depression and reduced food intake, decreased intestinal absorption of nutrients, altered nutrient metabolism, increased nutrient excretion, and internal diversion of nutrients (Beisel 1984). Additional nutritional losses occur with vomiting, diarrhea, sweating in fever, or loss of sputum in pneumonias. Liver damage caused by hepatitis can disrupt nutrient metabolism. Antimicrobial drugs may affect nutrient digestion and absorption or alter intestinal flora (Braude 1985). Many of these losses can be overcome by improved feeding methods (Siegel 1987).

## Hypermetabolism

*Acute-Phase Responses.* Acute-phase responses during acute infectious illnesses are of major nutritional importance because they involve many body functions and because they speed up the consumption of nutrients in the body and deplete nutritional stores (Beisel 1985). They result in general symptoms and signs of illness, including fever, loss of appetite, increase in numbers of white blood cells, heightened body metabolism, muscle pains and breakdown of skeletal muscle protein, use of some free amino acids from this breakdown for generating energy rather than for synthesizing new protein, altered metabolism of sugars and fats, redistribution of trace minerals, and stimulation of the immune system. The nutrient costs of these acute-phase responses depend on the severity and duration of the infectious process, the prior nutritional status of the patient, and the effectiveness of therapeutic interventions (NRC 1976; Beisel et al. 1977).

Acute-phase responses to infection are initiated by a common mechanism—the release of IL-1 and other hormone-like mediators from cells. The nutritional consequences of this release are similar regardless of the infecting organism. These include an increase in secretion of insulin and glucagon from pancreatic islets and alterations in the metabolism of carbohydrate, fat, and protein (Kluger, Oppenheim, and Powanda 1985; Dinarello 1985; Movat et al. 1987) that increase use and loss of body nutrients (Keusch 1984).

In some infections, especially those caused by gram-negative bacteria, body macrophages are stimulated by lipopolysaccharide toxins to release another hormone-like mediator. This mediator was initially termed cachectin, although it has proved to be tumor necrosis factor (TNF). Because TNF inhibits the membrane-bound enzyme lipoprotein lipase, it contributes to the accumulation of triglycerides in the plasma during gram-negative sepsis as well as to other alterations in body lipid metabolism. TNF also plays a role in the development of hypotensive shock during sepsis. Experimental evidence shows that TNF and IL-1 act synergistically, thereby amplifying the loss of body nutrients that lead to cachexia (Trac̄y et al. 1988).

*Fever.* Fever causes metabolic rates to increase about 7 percent for each increase of 1° F. This hypermetabolism affects all cells of the body. In addition, phagocytic cells increase their rate of oxygen consumption whenever they take up bacteria or other particles. Because this extra energy comes largely from amino acid metabolism (Siegel 1987; Bell et al. 1983), the body stores of muscle protein amino acids and nitrogen are rapidly depleted (Beisel 1985). Loss of nutrients may also occur through sweating



associated with fever. Controlling the infection minimizes fever and reduces losses of body nutrients.

*Loss of Appetite.* Severe loss of appetite is a common symptom during most infectious diseases and often leads to an almost total cessation in food consumption. Based on studies in laboratory animals, the effects of IL-1 and other monokines on the appetite centers in the brain may cause this anorexia (Kluger, Oppenheim, and Powanda 1985; Dinarello 1988).

*Reduced Absorption.* Vomiting, diarrhea, altered bowel motility, and infection-induced decreases in synthesis of intestinal enzymes further reduce the absorption of nutrients from the intestinal tract. Antibiotics and other medications also modify intestinal absorption and motility, as discussed in the chapter on drug-nutrient interactions.

#### Altered Metabolism

*Protein.* Some proteins break down (catabolize) and others are formed during acute-phase reactions, but the catabolic aspects predominate and lead to clinically evident losses of muscle mass and body nitrogen (Rennie and Harrison 1984). IL-1 induces the release of amino acids from contractile proteins (Kluger, Oppenheim, and Powanda 1985) and the preferential oxidation of branched-chain amino acids (leucine, isoleucine, valine) to provide metabolic energy in muscle. Alanine, synthesized in muscle from glucose and components of the branched-chain amino acids, is then taken up by the liver and used to manufacture glucose.

Despite the accelerated input into plasma of free amino acids from muscle, concentrations of most free amino acids are lowered because of increased use of body cells and reduced dietary intake due to loss of appetite. These free plasma amino acids are used to manufacture the new body cells and proteins needed for defense against infection. As described previously, the liver takes up large amounts of free plasma amino acids during infection and uses them to synthesize glucose and to make compounds that contribute to nonspecific host defenses (Powanda and Canonico 1981).

Excess nitrogen derived from these processes is metabolized to urea and excreted in urine, thereby accounting for most of the nitrogen lost during infection. Infection-induced nitrogen losses can be quite extensive. For example, malaria, which was once used as a form of therapy for neurosyphilis (Howard, Bigham, and Mason 1946), has caused extensive losses of body nitrogen and advanced cachexia in as little as 30 days. Even brief, self-limited viral infections and brief fevers induced by bacterial infections

can cause sizable losses of nitrogen (Beisel et al. 1977); although protein-nitrogen losses of mild or promptly treated infections do not lead to cachexia, they suggest that large losses of body protein can occur in even a week-long infection accompanied by fever. The magnitude of body protein catabolized can be quantitated roughly by the excesses of total nitrogen in the urine. The breakdown of contractile protein in skeletal muscle can be estimated by the amount of 3-methyl-histidine excreted in urine (Beisel 1985).

Although the catabolism of body proteins is a predominant feature of the acute-phase response, the anabolism of certain proteins is also stimulated. Proteins needed for the reproduction of white blood cells and immunoglobulins account for some of this anabolic activity. The liver is stimulated to synthesize a large number of proteins for intracellular use (e.g., enzymes and metallothionines) as well as a variety of proteins that enter the plasma. These include components of the complement system, the kinin system, and the coagulation system. Also synthesized within the liver are a group of plasma glycoproteins termed acute-phase reactants. In humans, these include haptoglobin, C-reactive protein, ceruloplasmin, alpha-antitrypsin, and orosomucoid, all of which appear to play some protective role during infection (Beisel 1985).

*Lipids.* During infections, hormonal influences on the liver lead to the synthesis of excessive amounts of free fatty acids (Powanda and Canonico 1981) and a reduction in the conversion of free fatty acids to ketones, a process that normally occurs during periods of reduced food intake. These phenomena lead to increased production of triglycerides, the accumulation of fat droplets within liver cells, and an increase in triglyceride concentrations in blood. These changes are especially pronounced in infections caused by endotoxin-containing bacteria, apparently because of the release of the monokine TNF, which inhibits lipoprotein lipases on cell walls (Beisel 1985). In addition, IL-1 is thought to activate phospholipase enzymes in cell walls that stimulate the production of arachidonic acid, which, in turn, is converted into prostaglandins or leukotrienes within body cells (Kluger, Oppenheim, and Powanda 1985).

*Vitamins.* Tissue and plasma concentrations of most vitamins have been reported to decline during infections, perhaps because of increased metabolism or excretion. The concentration of vitamin C, for example, declines in neutrophils and in the adrenal cortex during active steroid production, which may occur during the stress of illness. The accelerated metabolism or loss of vitamins during infections may precipitate recognizable deficiency states (Scrimshaw et al. 1968; Beisel 1985).

*Minerals.* During infection, all of the principal intracellular elements are lost from the body, roughly in proportion to the losses of nitrogen (Beisel 1985). Blood mineral concentrations decline slightly and may be severely reduced under certain circumstances. Calcium (in conjunction with calmodulin) is intimately involved in many altered molecular responses of body cells during febrile infections, but calcium is not generally lost from the body unless an infection causes muscle paralysis or requires prolonged bed rest. These mineral losses are readily replaced by supplying adequate intake during convalescence (Beisel 1985).

Responses induced by IL-1 also cause the redistribution of iron, zinc, and copper within the body. Both iron and zinc leave the plasma and are held in a storage form for as long as the infection persists. Zinc is held in hepatic cells by newly produced binding proteins (metallothionines), and iron is stored as ferritin or hemosiderin. In contrast, copper leaves the liver and accumulates in blood as a component of ceruloplasmin. This redistribution appears useful for host defenses against infection, although specific functions have not been established (Beisel 1982a).

Electrolyte metabolism is altered in most systemic infections by the renal retention of sodium and chloride and, therefore, of extracellular water. In some infections, especially those that localize in the brain, an inappropriate secretion of antidiuretic hormone causes more intense retention of body water and dilution of the electrolytes in body fluids (Beisel 1985). Conversely, significant quantities of sodium, chloride, and other nutrients may be lost through the sweating associated with fever and infection, and any infection that causes diarrhea will induce fecal losses of sodium, chloride, potassium, and bicarbonate, as well as water. Cholera, for example, induces extensive water and electrolyte losses from the gastrointestinal tract, and cholera deaths are from dehydration rather than from the infection itself. Such losses are especially dangerous in already malnourished infants and children (Beisel 1985).

#### AIDS: A New Example of Complex Infection-Nutrition-Immunity Interactions

AIDS (acquired immunodeficiency syndrome), caused by the human immunodeficiency virus (HIV), is a disease with multiple pathologies, most of which are the consequence of a profound immunodeficiency. The CD4-bearing T lymphocytes appear to be the primary population of target cells that are lost in HIV-infected patients. This loss includes the majority of helper T cells that help killer T cells and B cells function properly. Therefore, killer cell function is reduced, which leads to a loss of recognition and

elimination of body cells infected with other micro-organisms. Reduced B cell function disables the body's ability to make new antibodies for the neutralization or elimination of micro-organisms located in extracellular body fluids. In addition, there is a profound loss of the lymphokine mediators normally produced by helper T cells. This loss reduces the activation of macrophages and the maturation and effectiveness of natural killer cells that help combat infections and cancer (Weissman 1988).

Weight loss and deteriorating nutritional status are critical features of the AIDS disease process (Anonymous 1985; Kotler, Wang, and Pierson 1985). Anorexia, nausea and vomiting, fever, and diarrhea are common features of advanced AIDS, as are malabsorption of fats, carbohydrates, and protein and some intestinal injury and dysfunction (Garcia, Collins, and Mansell 1987; Kotler 1987). The underlying causes of these gastrointestinal symptoms include infections by viral, parasitic, or bacterial pathogens as well as disseminated Kaposi's sarcoma. Even before recognition of AIDS, several research groups reported unique and multiple enteric pathogens in homosexual men (Quinn et al. 1983; Baker and Peppercorn 1982). These infections are strongly associated with depressed appetite, decreased food intake, and severe wasting typical of illness-induced malnourished states (Kotler, Wang, and Pierson 1985; O'Sullivan, Linke, and Dalton 1985).

As noted earlier, such severe malnutrition is associated with impaired function of specific components of the immune system and a generalized reduction in the energy resources needed to support cell growth and proliferation. The similarity of immune abnormalities resulting from malnutrition and those seen in AIDS has led to suggestions that malnutrition might predispose to AIDS or that nutritional therapy might improve immune status and prevent AIDS (Jain and Chandra 1984) or improve its prognosis (Kotler 1987). Little evidence, however, supports either of these suggestions. Although the most severely malnourished AIDS patients are at highest risk, severe malnutrition is more likely to be a result of AIDS-related intestinal injury than a cause of this condition. As in other conditions, correction of malnutrition would be expected to improve response to therapy and to decrease susceptibility to opportunistic infections, but complications of intravenous nutritional support—electrolyte imbalances, excessive concentrations of blood sugar and fat, and infections of the intravenous access routes—have made it difficult to test these hypotheses in AIDS patients (Kotler 1987). Although some preliminary studies have observed improved weight maintenance in AIDS patients receiving nutritional support (Domaldo and Natividad 1986), others indicate that weight gain is due to water retention rather than to repletion of body cell mass

(Kotler, Wang, and Pierson 1985; Kotler 1987). To date, suggestions that AIDS-specific immune dysfunctions can be either arrested or reversed by nutritional therapy are not supported by clinical or biochemical evidence (Kotler 1987).

#### Nutritional Rehabilitation

The early convalescent period following a serious infection is an important time to restore normal metabolic processes and replenish energy reserves. Frequently, this period is accompanied by a marked hunger. An appropriate refeeding program can replace nutrient losses rapidly and stimulate the recovery of normal host defensive and immunologic functions. However, nutritional support for severely wasted patients with infections is often difficult (Siegel 1987; Bell et al. 1983) because of nutrient imbalances and other complications (Baron 1986) and because of insufficient knowledge of the actions, or side effects, of nutrients administered parenterally (Siegel 1987). Other problems are caused by severe weaknesses of the respiratory musculature in wasted patients (Bell et al. 1983), who may be unable to get rid of the large quantities of carbon dioxide produced when extra energy sources are provided to the body. Further research is needed to develop more effective methods to overcome malnutrition induced by severe infectious diseases.

#### **Role of Diet-Immune System Relationships in Food-Associated Illnesses**

Adverse reactions to food involve both immunologic and nonimmunologic mechanisms. Immunologic reactions are known commonly as food allergies. Nonimmunologic intolerances include those that are biochemical (food toxicities, poisonings, and digestive disorders) or psychologic. Foods may also transmit micro-organisms that cause infectious illnesses. The numerous causes of food-associated illness are listed in Table 11-1.

#### Immunologic Mechanisms (Allergies)

Although the immune system usually protects the body against foreign substances, antigen-specific immune responses can sometimes produce adverse, even fatal, effects. Food is the largest antigenic challenge confronting the human immune system (Sampson, Buckley, and Metcalfe 1987). Food allergies are examples of the negative consequences of immune function on the gastrointestinal tract, skin, lungs, and other organ systems. Symptoms can include acute abdominal pain, swelling, nausea, vomiting, rashes, vascular collapse, chronic itching, headache, tension, and fatigue. Eczema, asthma, and rhinitis are more common in children than in adults (Metcalfe 1985).

**Table 11-1**  
**Causes of Food-Associated Illness**

| Food-borne Infections<br>Due to: | Food Origin Toxemias<br>Due to: | Food Allergies<br>Due to: | Nonallergic Food Intolerances  |                   |
|----------------------------------|---------------------------------|---------------------------|--------------------------------|-------------------|
|                                  |                                 |                           | Due to Natural Products:       | Due to Chemicals: |
| Bacteria                         | Botulinum toxins                | Milk                      | Lactose                        | Sulfites          |
| Salmonella                       | Staphylococcal                  |                           | Sucrose                        | Nitrites          |
| Shigella                         | Enterotoxins                    | Eggs                      | Galactose                      | Nitrates          |
| Campylobacter                    | <i>Escherichia coli</i>         |                           | Gluten                         | Monosodium        |
| <i>Escherichia coli</i>          | Enterotoxins                    | Wheat                     | Borad beans<br>(favism)        | glutamate         |
| <i>Vibrio parahemolyticus</i>    | Verocytotoxins                  |                           | Laythyrus peas<br>(laythyrism) | Tartrazine dyes   |
| <i>Listeria monocytogenes</i>    | Clostridial                     | Peanuts                   | Caffeine                       | Benzoic acid      |
| Yersinia                         | Perfringen toxins               |                           | Theobromine                    | Organophosphates  |
|                                  | Difficile toxins                | Soybean<br>products       | Histamine                      | Oxalates          |
| Parasites                        | <i>Bacillus cereus</i>          |                           | Tyramine                       | Heavy metals      |
| Trichinella                      | Enterotoxins                    | Nuts                      | Tryptamine                     | Mercury           |
| Toxoplasma                       |                                 |                           | Serotonin                      | Lead              |
| Amoeba                           | Mushroom toxins                 | Fish                      |                                | Arsenic           |
| Giardia                          |                                 |                           |                                | Copper            |

|                            |                       |             |                  |                |
|----------------------------|-----------------------|-------------|------------------|----------------|
| Isosporia (Coccidia)       | Fungal toxins         |             | Phenylethylamine | Aspartame      |
| Cryptosporidia             | Ergot, mycotoxins     | Shellfish   | Solamine         | Butylated-     |
|                            | Trichothecenes        |             |                  | hydroxytoluene |
| Viruses                    | Aflatoxins            | Other foods |                  | hydroxyanisole |
| Hepatitis A virus          |                       |             |                  |                |
| Norwalk agent              | Puffer fish           |             |                  |                |
| Other Norwalk-like         | Tetrodotoxin          |             |                  |                |
| viruses                    | Ciguatoxins           |             |                  |                |
| Rotaviruses                | Scrombroid fish toxin |             |                  |                |
| Adenoviruses <sup>a</sup>  | Shellfish saxitoxin   |             |                  |                |
| Astroviruses <sup>a</sup>  |                       |             |                  |                |
| Echoviruses                |                       |             |                  |                |
| Snow Mountain agent        |                       |             |                  |                |
| Cockle agent               |                       |             |                  |                |
| Coxsackie B viruses        |                       |             |                  |                |
| Caliciviruses <sup>a</sup> |                       |             |                  |                |

---

<sup>a</sup>Viruses that cause gastroenteritis and may be food borne.

To distinguish a true allergic reaction from an intolerance due to a biochemical or psychologic disturbance, the specific food causing the reaction must be clearly identified, a proper diagnostic procedure followed, and the cessation of symptoms documented when the offensive food is eliminated. A scientifically rigorous diagnosis requires additional diagnostic tools such as the Radioallergosorbant Test (RAST), the Enzyme Linked Immunosorbant Assay (ELISA), and skin testing (although all of these are of limited value), elimination diets, and double-blind food challenges (Sampson, Buckley, and Metcalfe 1987). The efficacy of cytotoxic testing, provocative subcutaneous testing, and provocative sublingual tests of food extracts to diagnose food hypersensitivity are unproved, and use should be limited to well-constructed diagnostic trials. At present, no single diagnostic test appears to be definitive in the diagnosis of food allergy (AAAI 1984).

Allergic reactions are caused by an adverse interaction between a protein antigen and an IgE immunoglobulin antibody. The IgE antibody first binds to the surface of a mast cell, a cell that is capable of releasing histamines and other factors. This binding prepares the mast cell for subsequent binding of a food antigen, which, in turn, triggers the cell to release histamine and other vasoactive mediators that produce the signs and symptoms of food allergies (AAAI 1984). This type of allergic hypersensitivity occurs within minutes to hours and, in rare instances, can be life threatening. The molecules of several antigens in foods capable of triggering mast cell reactions have been isolated and their structures identified (Moroz and Yang 1980; Metcalfe 1985).

The most common foods to which people are allergic are egg, milk, wheat, peanut, soybean, chicken, fish, shellfish, and nuts (Atkins 1983). Responses to such foods are not always consistent, however, because they depend on the amount and form of the food consumed and the presence of other foods in the diet or of medications. Thus, foods that have not caused reactions in the past may induce allergic responses when other mitigating factors are present (Atkins 1983).

Estimates of the incidence of food allergies in infants range from 0.3 percent to 20 percent. Because allergies tend to be outgrown, the incidence decreases to less than 3 percent in adults (Butkus and Mahan 1986; Bock and Martin 1983). Because only about one-fourth of histories of adverse food reactions can be confirmed by diagnostic tests (May 1980; AAAI 1984), these estimates may be too high (IFT 1986).