

Nutrition and the immune system: an introduction¹⁻³

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ABSTRACT Nutrition is a critical determinant of immune responses and malnutrition the most common cause of immunodeficiency worldwide. Protein-energy malnutrition is associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobulin A antibody concentrations, and cytokine production. Deficiency of single nutrients also results in altered immune responses: this is observed even when the deficiency state is relatively mild. Of the micronutrients, zinc; selenium; iron; copper; vitamins A, C, E, and B-6; and folic acid have important influences on immune responses. Overnutrition and obesity also reduce immunity. Low-birth-weight infants have a prolonged impairment of cell-mediated immunity that can be partly restored by providing extra amounts of dietary zinc. In the elderly, impaired immunity can be enhanced by modest amounts of a combination of micronutrients. These findings have considerable practical and public health significance. *Am J Clin Nutr* 1997;66:460S-3S.

KEY WORDS Protein-energy malnutrition, immunity, cell-mediated immunity, micronutrients, low-birth-weight infants, elderly

INTRODUCTION

It is now generally accepted that nutrition is an important determinant of immune responses. Epidemiologic and clinical data suggest that nutritional deficiencies alter immunocompetence and increase the risk of infection. Poor sanitation and personal hygiene, overcrowding, contaminated food and water, and inadequate nutrition knowledge contribute to this susceptibility. Work done in the past 25 y has confirmed that impaired immunity is a critical adjunct factor in malnutrition-associated infection. This concept applies not only to young children in developing countries but also to all age groups in all populations of the world, including the elderly, those with eating disorders, and patients with a variety of primary debilitating diseases. A list of reviews and monographs is provided for further reading and citations to specific findings (1-13).

THE IMMUNE SYSTEM

Detailed descriptions of the immune system and its dysfunction in primary and secondary immunodeficiency disorders can be found elsewhere (14, 15). Host resistance mechanisms can be divided into two main tiers: nonspecific and antigen specific (**Figure 1** and **Figure 2**). The nonspecific defenses include the skin and mucous membranes, phagocytic cells, mucus, cilia,

complement, lysozyme, interferon, and other humoral factors. These innate processes are naturally present and are not influenced by prior contact with the infectious agent. They act as the first line of protection and retard the establishment of overt infection. Antigen-specific mechanisms include the B cell system of antibody production and the T cell system of cell-mediated immunity. These mechanisms are adaptive and acquired in that they are specific reactions induced by prior exposure to the microorganism or its antigenic determinants. They are effective in checking the spread of infection and eradicating the invading organism. The specific immune responses form the basis of prophylactic immunization against common communicable diseases such as measles, respiratory illness caused by *Hemophilus influenza*, and systemic disease caused by *Salmonella*. In the body, nonspecific and antigen-specific defenses act in concert.

PROTEIN-ENERGY MALNUTRITION

Lymphoid atrophy is a dramatic feature of protein-energy malnutrition (PEM). The size and weight of the thymus are reduced. Histologically, there is a loss of corticomedullary differentiation; there are fewer lymphoid cells; and the Hassall bodies are enlarged, degenerated, and occasionally calcified. These changes are easily differentiated from findings in primary immunity deficiency, such as DiGeorge syndrome (14, 15). In PEM there is also a loss of lymphoid cells around small blood vessels in the spleen and in lymph nodes the thymus-dependent paracortical areas show depletion of lymphocytes.

In PEM most host-defense mechanisms are impaired. Delayed-hypersensitivity cutaneous responses both to recall and new antigens are markedly depressed. It is not uncommon to have complete anergy to a battery of different antigens. These changes are observed in moderate deficiencies as well. The skin reactions are restored after appropriate nutritional therapy for several weeks or months. There is also a reduction in mature, fully differentiated T lymphocytes due in part to a

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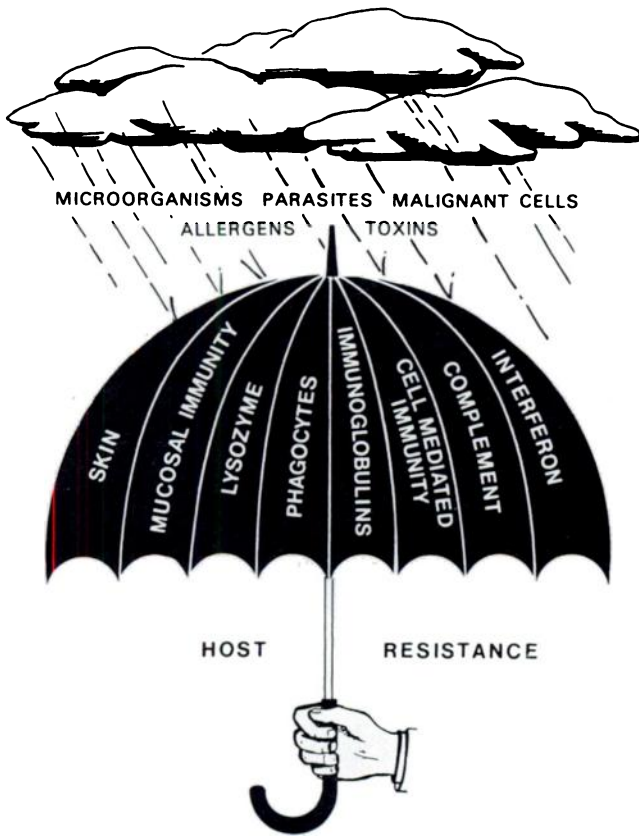


FIGURE 1. A simple view of host defenses as a protective umbrella, consisting of physical barriers (skin and mucous membranes), nonspecific mechanisms (complement, interferon, lysozyme, and phagocytes), and antigen-specific processes (antibodies of five immunoglobulin isotypes and cell-mediated immunity). Reproduced with permission from ARTS Biomedical Publishers (12).

reduction in serum thymic factor activity. Additionally, deoxy-nucleotidyl transferase activity in leukocytes is increased. The proportion of helper inducer T lymphocytes recognized by the

presence of CD4+ antigen on the cell surface is markedly decreased (**Figure 3**). There is also a moderate reduction in the number of suppressor cytotoxic CD8+ cells. Thus, the ratio of CD4+ to CD8+ cells is significantly lower than that in well-nourished control subjects. Moreover, co-culture experiments showed a reduction in the number of antibody-producing cells and in the amount of immunoglobulin secreted. This may largely be due to decreased help provided by T lymphocytes (**Figure 4**). Lymphocyte proliferation and DNA synthesis are shown to be reduced, especially when the autologous plasma from a patient is used in cell cultures. This may be the result of inhibitory factors as well as deficiency of essential nutrients in the patient's plasma.

Serum antibody responses are generally intact in PEM, particularly when antigens in adjuvant are administered or for materials that do not evoke T cell response. Antibody affinity, however, is decreased in patients who are malnourished. This may provide an explanation for a higher frequency of antigen-antibody complexes found in such patients. Secretory immunoglobulin A (sIgA) antibody concentrations are lower after immunization with viral vaccines; there is a selective reduction in sIgA concentrations with some compensatory increase in IgM concentrations in secretions. This may have several clinical implications, including an increased frequency of septicemia commonly observed in undernourished children.

Phagocytosis is also affected in PEM. Complement is an essential opsonin and the concentrations and activity of most complement components are decreased. The best documented is a reduction in C3, C5, factor B, and total hemolytic activity. There is a slight reduction in opsonic activity of plasma. Furthermore, metabolic activation and intracellular destruction of bacteria are reduced. Finally, recent work in humans and animals showed that the production of several cytokines, including interleukins 1 and 2 and interferon γ , is decreased in PEM. Moreover, malnutrition alters the ability of T lymphocytes to respond appropriately to cytokines. There is little work on the effect of malnutrition on the integrity of physical barriers, quality of mucus, or several other innate immune de-

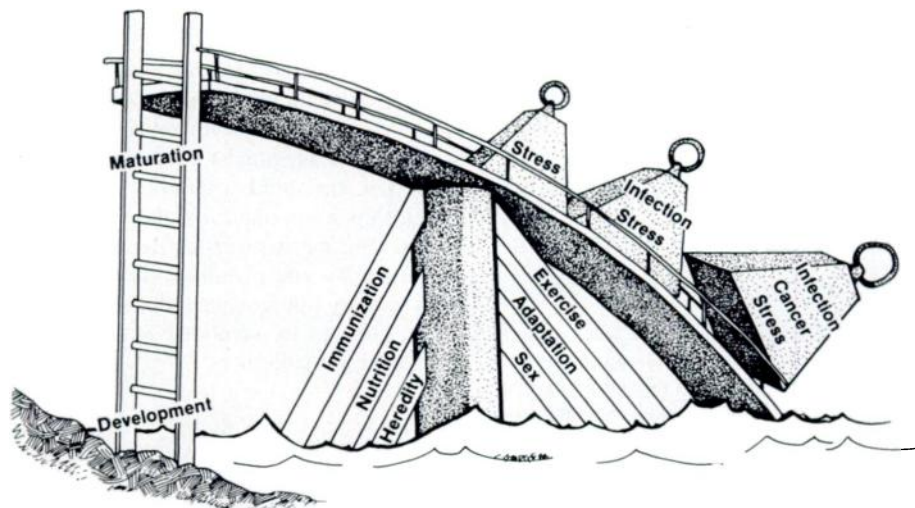


FIGURE 2. The immune system is a bridge of life. During fetal and early postnatal life, it undergoes development and maturation. Heredity, sex, adaptation, exercise, immunization, and nutrition are important determinants. Stress, infection, and diseases such as cancer can impair further immunity and end in a fatal outcome. Reproduced with permission from ARTS Biomedical Publishers (12).

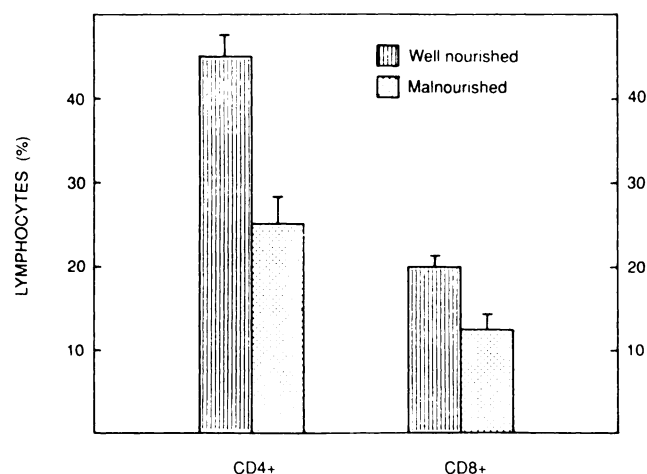


FIGURE 3. The proportion of two subsets of T lymphocytes. There is a marked reduction in the proportion of CD4+ helper inducer cells in malnourished children ($P < 0.001$). Differences between the two groups for CD8+ cytotoxic suppressor cells are less but are significant ($P < 0.05$). Reproduced with permission from the American Society for Clinical Nutrition (2).

fenses. For example, lysozyme concentrations are decreased, largely as the result of reduced production by monocytes and neutrophils and increased excretion in urine. Adherence of bacteria to epithelial cells is an essential first step before invasion and infection can occur. The number of bacteria adhering to respiratory epithelial cells is increased in PEM.

MICRONUTRIENTS

Several trace elements and vitamins have an essential role in key metabolic pathways and immune cell functions. Isolated deficiencies of micronutrients are rare with the exception of iron, vitamin A, and zinc. However, they frequently complicate PEM and many systemic diseases. Moreover, human malnutrition is

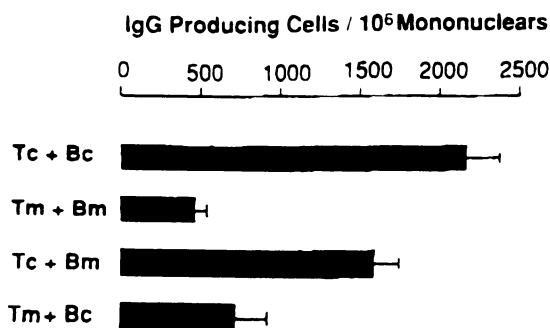


FIGURE 4. Immunoglobulin G (IgG) production in co-culture experiments in which T and B lymphocytes are mixed and stimulated with pokeweed mitogen for 7 d. IgG-producing cells are recognized by lytic areas in a reverse hemolytic plaque assay. Compared with well-nourished control subjects (Tc + Bc), there is a marked reduction in the number of antibody-producing cells in malnourished children (Tm + Bm). When T cells of healthy control subjects (Tc) are mixed with B cells of malnourished patients (Bm), there is a significant improvement in response, whereas the opposite combination (Tm + Bc) results in a moderate increase. Reproduced with permission from the American Society for Clinical Nutrition (2).

usually a composite syndrome of multiple nutrient deficiencies. Observations in laboratory animals deprived of one dietary element and findings in the rare patient with a single nutrient deficiency have confirmed the crucial role of several vitamins and trace elements in immunocompetence. Detailed description of the effect of micronutrients on immune responses is given elsewhere (11). Five general concepts have been advanced. First, alterations in immune responses occur early in the course of reduction in micronutrient intake. Second, the extent of immunologic impairment depends on the type of nutrient involved, its interactions with other essential nutrients, the severity of deficiency, the presence of concomitant infection, and the age of the subject. Third, immunologic abnormalities predict outcome, particularly the risk of infection and mortality. Fourth, for many micronutrients excessive intake is associated with impaired immune responses and, finally, tests of immunocompetence are useful in titration of physiologic needs and in assessment of safe lower and upper limits of micronutrient intake.

Zinc is chosen as an example to illustrate these concepts. Zinc deficiency, both acquired and inherited, is associated with lymphoid atrophy, decreased delayed-hypersensitivity cutaneous responses, delayed homograft rejection, and lower thymic hormone activity. Patients with acrodermatitis enteropathica have impaired lymphocyte response to phytohemagglutinin, decreased thymulin activity, and reduced delayed-hypersensitivity cutaneous reactions. In laboratory animal models these findings can be confirmed and, in addition, one can show a reduced number of antibody-forming cells in the spleen and impaired activity of T killer cells, decreased ingestion, and reduced phagocytosis. Zinc is probably involved in stimulation of NADPH oxidase through its role as a cofactor for phospholipase A2 or phospholipase C. Zinc may stabilize arachidonic acid against oxidation by iron complexes. Zinc complexes may react with oxygen, generating products highly toxic to ingested pathogens. Wound healing is impaired in zinc deficiency. Zinc deficiency increases morbidity and mortality of animals challenged with various organisms, including *Enterovirus coxsackie B* and *Listeria monocytogenes*. Zinc deficiency promotes the establishment of nematodes and alters the characteristics of their expulsion from the intestine although spontaneous cure is unaffected.

Important work needs to be done on the molecular basis of impaired lymphocyte and phagocyte functions in zinc deficiency. A slight excess intake of certain nutrients such as zinc may be associated with enhanced immune responses. It is known now that almost all nutrients given in quantities beyond a certain threshold will reduce immune responses. This has been shown for zinc for both phagocyte and lymphocyte functions. The mechanisms of these immunotoxic effects are not clear, but for zinc overdose, alterations in serum and cell-bound low-density lipoproteins reduced concentrations of other nutrients; changes in membrane structure and receptor expression are some possibilities.

THE ELDERLY

There is much recent interest in and work on the effects of dietary intake and nutritional status on immunity and risk of illness in old age. The pattern of illness observed in the elderly suggests that immune responses decline in old age. Because of

the close contact of the immune system with other systems in the body, any changes in immunocompetence can be expected to influence other organ functions as well. As immunologic vigor declines, incidences of infections, cancer, immune complex disease, autoimmune disorders, and amyloidosis increase. Cellular and molecular manipulation including nutritional support to prevent or slow the decline of immune functions can be expected to delay the onset or decrease the severity of pathology associated with aging.

Age-related changes in immune responses have been the focus of much recent work. The number of pluripotent cells with the ability to colonize peripheral lymphoid sites and to mature into competent cells decreases with age. The ability of stem cells to undergo clonal proliferation decreases and the generation of B cells and homing of precursor cells into the thymus is reduced. This restraint on stem cell kinetics and reserves may be critical to an effective response to stress, such as infection. Elderly patients with sepsis often fail to mount leukocytosis, although the expected shift to the left of immature polymorphonuclear leukocytes does occur.

In the elderly, delayed-hypersensitivity cutaneous responses to ubiquitous recall antigens derived from bacterial and fungal products, as well as to 2,4-dinitrochlorobenzene, are reduced in frequency and in size. Lymphopenia and anergy have important prognostic significance in old age. The number of circulating T lymphocytes is slightly decreased. The number of CD4+ cells is decreased, whereas the number of CD8+ cells is variously reported as normal, decreased, or increased. Functional alterations associated with these changes in the number of cells include decreased lymphocyte proliferation in response to mitogens and antigens, reduced production of macrophage migration inhibition factor and of interleukin 2, impaired mixed lymphocyte reaction, and decreased natural killer cell activity. There is also a sharp decline in thymulin activity. There is a reduction in serum IgG concentration and an increase in serum IgA. Generally, primary antibody response is decreased but antibody titer after booster immunization is often comparable in the young and the elderly. There is, however, a delay in reaching the peak antibody response in the elderly.

For many antigens, antibody production by B cells requires helper factors generated by T cells. Antibody responses to such antigens are decreased in old age and the affinity of the antibody may be reduced. There are no data on sIgA antibody responses of old individuals. Polymorphonuclear leukocytes obtained from the elderly have reduced migration ability, both random and chemotactic. The uptake of microorganisms is slightly reduced and has been attributed to a more rigid cell membrane. There is partial reduction in the magnitude of the metabolic burst associated with phagocytosis, and lysis of *Candida* is impaired.

Nutritional deficiencies are seen in at least one-third of the elderly in industrialized countries. Certain old individuals are at particularly high risk of malnutrition: the physically isolated; those living alone, especially those who have been recently bereaved; the socially isolated; those with sensory or mental impairment; those with a chronic systemic disease; the very poor; and the very old. Furthermore, a reduction in total energy intake results in inadequate consumption of certain essential nutrients. This is further compounded by a lack of variety and characteristic self-selection of food items, the presence of malabsorption in some elderly individuals, and drug-nutrient interactions.

The simultaneous assessment of nutritional status and immune responses and subsequent correlation analysis have suggested that impaired immunity in the elderly may be due in part to associated nutritional deficiencies. Several recent studies attempted to correct nutritional deficiencies in the elderly and examined the effects of such interventions on immune responses (1). In general, providing extra energy or multiple micronutrients or moderately large doses of single nutrients resulted in improved immune responses. In a few studies, this was associated with reduced infection-related illness. Much more work needs to be done in this area of considerable public health significance.

CONCLUDING REMARKS

The well-established effect of nutrition on immunity has led to several practical applications. These include the use of immunologic tests as prognostic indexes in patients undergoing surgery and the use of immunologic methods to assess nutritional status (13) and to judge the adequacy of nutritional therapy and improved immunologic response to and protective efficacy of vaccines. Finally, this new knowledge has permitted the development of designer feeding formulas with selective ingredients in specified amounts; these feeding formulas have been shown to reduce the risk of infection in animal models and in immunocompromised hosts (1). Clearly, the work on nutrition and immunity reviewed here has had a significant and crucial influence on public health and clinical medicine. ■

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