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The Interaction between Nutrition and Infection

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Infection and malnutrition have always been intricately linked. Malnutrition is the primary cause of immunodeficiency worldwide, and we are learning more and more about the pathogenesis of this interaction. Five infectious diseases account for more than one-half of all deaths in children aged <5 years, most of whom are undernourished. Micronutrient deficiencies have effects such as poor growth, impaired intellect, and increased mortality and susceptibility to infection. The worldwide magnitude of parasite infection is enormous. It is understood that parasites may lead to malnutrition, but the extent to which malnutrition causes increased parasite infestation is not known; thus, the conditions need to be addressed together. Nutritional deficiencies associated with pregnancy are associated with poor immune response to infection. Because this immune deficiency is partially compensated by breast-feeding, this is the single best way to protect infants from infection. Malnutrition and nutritional alterations, common complications of human immunodeficiency virus infection, include disorders of food intake, nutrient absorption, and intermediary metabolism and play a significant and independent role in morbidity and mortality. The 21st century provides new information and new challenges. With new technologies and political changes, it is hoped that a healthier, more disease-free, and better-nourished population will emerge.

Approximately 826 million people in the world are undernourished—792 million people in the developing world and 34 million in the developed world [1]. John Mason and colleagues [2] claimed that 32% of the global disease burden could be removed by eliminating malnutrition, whereas others have concluded that even this figure is a gross understatement [3–5], especially with the emergence of HIV/AIDS. Undernutrition is not necessarily caused by a lack of food, and it is not unique to poor populations. Even in rich nations, there are malnourished people. In the United States, for example, undernutrition affects up to 15% of ambulatory outpatients, 25%–60% of patients receiving long-term care, and 35%–65% of hospitalized patients [6].

Malnutrition is the primary cause of immunodeficiency worldwide, with infants, children, adolescents, and the elderly most affected. There is a strong relationship between malnutrition and infection and infant mortality, because poor nutrition leaves children underweight, weakened, and vulnerable to infections, primarily because of epithelial integrity and inflammation (figure 1) [7]. Five infectious diseases—pneumonia, diarrhea, malaria, measles, and AIDS—account for more than one-half of all deaths in children aged <5 years (figure 2) [8]. In our understanding of this interaction between infection and malnutrition, it is important to remember that a decreased immune function is not always a defective one, and many indicators of nutritional status are not reliable during infection.

THE MACRONUTRIENT ERA

During the 1950s, little was known about the link between nutrition and infection. Until that time, it was believed that protein deficiency (kwashiorkor), more than total calorie deficiency (marasmus), was the predominant basis of nutrition problems, because severe protein deficiency bore a definite relationship to antibody formation and the development of the immune system in infants and children. The focus then changed to energy, with the assumption that if a person consumed enough kilocalories of energy, all nutrient needs would be met.

On the basis of work done in Central America, Mexico, Chile, and South Africa, research after 1959 on the interaction of nutrition, immunity, and infection advanced with the work of Keusch [10] and Scrimshaw et al. [11], which showed extensive, synergistic, antagonistic, and cyclical interactions between malnutrition and infection. This suggested that a dual attack was

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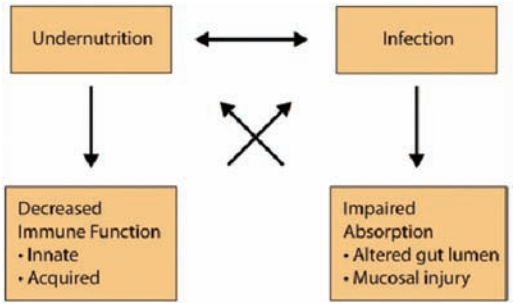

Figure 1. Interactions between malnutrition and infection

necessary. In 1968, the World Health Organization published "Interactions of Nutrition and Infection," which suggested that the relationship between infection and malnutrition was a synergistic one [11]. In the 1970s, the metabolic consequences of infection and the relationship between malnutrition and cell-mediated immunity were initially elucidated [12–16]. Consequently, advances between 1970 and 1980 brought improved tools to assess immune function, the complement system, mucosal immunity, and cell-mediated immune responses. Human studies and better animal models led to the recognition that malnutrition is not unique to children.

THE CYCLE OF MALNUTRITION AND INFECTION

Malnutrition can make a person more susceptible to infection, and infection also contributes to malnutrition, which causes a vicious cycle (figure 3). An inadequate dietary intake leads to weight loss, lowered immunity, mucosal damage, invasion by pathogens, and impaired growth and development in children. A sick person's nutrition is further aggravated by diarrhea, malabsorption, loss of appetite, diversion of nutrients for the immune response, and urinary nitrogen loss, all of which lead to nutrient losses and further damage to defense mechanisms. These, in turn, cause reduced dietary intake. In addition, fever increases both energy and micronutrient requirements. Malaria and influenza, for example, have mortality rates proportionate to the degree of malnutrition [17].

The causes of malnutrition and disease operate at different levels. The factors responsible are household food availability, personal health, health services, and the psychosocial care environment (figure 4). The existing primary health care infrastructure includes the types of services provided and the accessibility of health care (distance and affordability). Underlying the problem of malnutrition and disease is inadequate household food security, which the US Department of Agriculture defines as "access by all members at all times to enough food for an active, healthy life," not merely as adequate food for survival [18, p. 1]. Access to health services and environmental health conditions relate to essential drugs and immunizations, safe water, sanitation, and housing. Insufficient or delayed treatment also prolongs disease occurrence and severity.

Many of the basic causes of malnutrition also emerge at the national and international levels and relate to the availability and control of food. The political ideology of the ruling government and its commitment to preventing infectious disease and malnutrition affects the health of its entire population. Famine, for example, is a disaster caused not only by agricultural failures or natural disasters but too often by politics. Sen [19] has shown that political factors are responsible for nearly all famines. Even with the droughts in Ethiopia and West Bengal, it was government policy, not agricultural failure, that was responsible for the human crisis [19].

Food supply, underlying health, and health care interact in important ways, and their combined effect is synergistic. The underlying causes may also change with the seasons. Rural households, for example, may experience an annual hunger season. Diarrheal diseases and malaria are more prevalent during rainy seasons, and respiratory tract infections are more prevalent during cold weather.

MICRONUTRIENTS AND IMMUNITY

Worldwide, ~2 billion people are affected by micronutrient deficiencies, including vitamins A, C, and E and minerals zinc, iron, and iodine. The effects are poor growth, impaired intellect, and increased mortality and susceptibility to infection. Micronutrients have a relationship to antibody formation and the development of the immune system. These ill effects are preventable by supplements, fortification, and diet change. The Copenhagen Consensus [20] project on hunger and malnutrition even suggested that efforts to provide vitamin A, iron, iodine, and zinc generates higher returns than do trade liberalization or malaria, water, and sanitation programs.

Vitamin A maintains the integrity of the epithelium in the respiratory and gastrointestinal tracts. The World Health Organization estimates that, worldwide, 100–140 million children are vitamin A deficient, causing 1.2–3 million deaths per year [21]. Vitamin A deficiency increases the risk of diarrhea, *Plasmodium falciparum* malaria, measles, and overall mortality. Although we have come a long way since then, in 1968, Scrimshaw et al. concluded that "no nutritional deficiency is more consistently synergistic with infectious disease than that of vitamin A" [11, p. 64].

Vitamin A deficiency and measles, which is estimated to kill 2 million children per year, are closely linked. Measles in a child is more likely to exacerbate any existing nutritional deficiency, and children who are already deficient in vitamin A are at much greater risk of dying from measles. Postmeasles diarrhea is particularly difficult to treat and has a very high mortality [22]. Vitamin A deficiency increases the risk of developing respiratory disease and chronic ear infections [22]. Vitamin A sup-

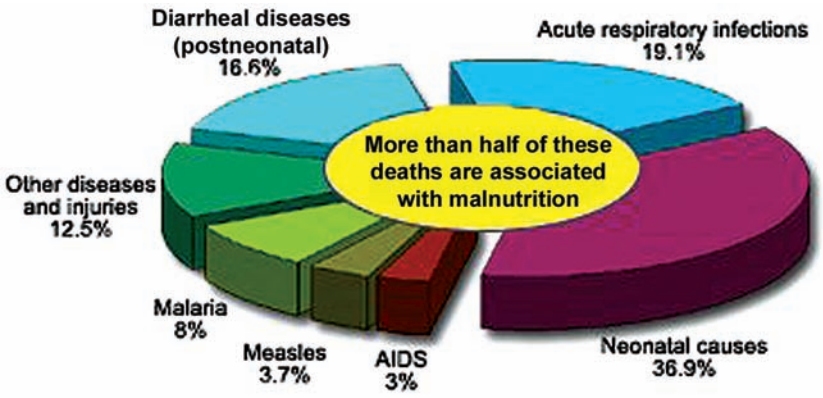

Figure 2. Causes of death in children aged <5 years, 2000–2003 [9]

plementation sustains gut integrity, lowers the incidence of respiratory tract infections, reduces mortality from diarrhea, and enhances immunity. Measles also depletes the body's supply of vitamin A. Thus, vaccination against measles often includes a high dose of vitamin A.

Vitamin E is an antioxidant that scavenges free radicals. Vitamin E supplementation has been shown to improve immune function in the elderly, with delayed hypersensitivity skin response and antibody production after vaccination. Vitamin E increases both cell-dividing and interleukin-producing capacities of naive T cells but not of memory T cells. This enhancement of immune function is associated with significant improvement in resistance to influenza virus infection in aged mice and a reduced risk of acquiring upper respiratory infections in nursing home residents [23].

Vitamin D supplements may offer a cheap and effective immune system boost against tuberculosis [24]. Vitamin D was used to treat tuberculosis in the preantibiotic era, when special sanatoria were built in sunny locations, such as the Swiss Alps. Investigators reported that a single 2.5-mg dose was sufficient to enhance the immune system's ability to withstand infection. These findings came from a study that identified an extraordinarily high incidence of vitamin D deficiency among tuberculosis-susceptible women in Muslim communities in London [25].

Zinc is a trace mineral that is essential for all species and is required for the activities of >300 enzymes, carbohydrate and energy metabolism, protein synthesis and degradation, nucleic acid production, heme biosynthesis, and carbon dioxide transport. It is a cofactor in the formation of enzymes and nucleic acids and plays a critical role in the structure of cell membranes and in the function of immune cells. Zinc deficiency reduces nonspecific immunity, including neutrophil and natural killer cell function and complement activity; reduces numbers of T and B lymphocytes; and suppresses delayed hypersensitivity, cytotoxic activity, and antibody production.

Inadequate zinc supply prevents normal release of vitamin A from the liver; clinically, it is associated with growth retardation, malabsorption syndromes, fetal loss, neonatal death, and congenital abnormalities. Low blood zinc concentrations have also been found in patients with tuberculosis, Crohn disease, diarrheal disease, and pneumonia. Zinc deficiency is associated with abnormal pregnancy outcomes [26] and conditions of relative immunocompromise, including alcoholism, kidney disease, burns, inflammatory bowel disease, and HIV infection. Many drugs, including corticosteroids, also cause excessive excretion.

Zinc supplementation reduces the duration and intensity of diarrheal illness and pneumonia among children living in developing nations. It limits growth stunting in children affected by acute diarrheal illness and reduces clinical disease caused by *P. falciparum* [27, 28]. In patients with sickle cell disease, it increases IL-2 production and decreases the number of infections and hospitalizations [29–31]. A weekly dose of 70 mg not only reduced the incidence of and prevented death of pneumonia but also had an effect on the incidence of diarrhea, with overall mortality reduced by 85% [32]. Resistance to infection and improved appetite were found with continuous potassium and magnesium as well as zinc supplementation [33, 34].

Iron deficiency is the most common trace element deficiency worldwide, affecting 20%–50% of the world's population, mainly infants, children, and women of childbearing age [36]. It is associated with impairments in cell-mediated immunity and reductions in neutrophil action, with decreased bacterial and myeloperoxidase activity. It lowers the body's defenses against disease and diminishes body and brain functions. Despite this, iron deficiency has unclear effects on infectious disease risk.

In the treatment of malaria, correcting iron deficiency is important, because malaria causes hemolysis and anemia. Supplementation in some cases, however, may actually aggravate infection, because the malaria parasite requires iron for its mul-

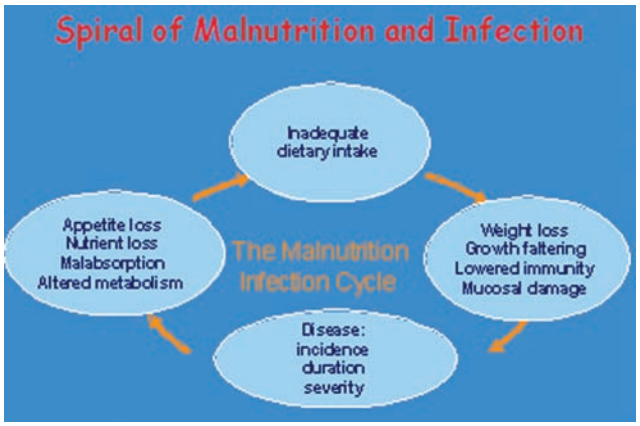

Figure 3. The "vicious cycle" of malnutrition and infection

tiplication in blood and thus may be less infective in the iron-deficient person. The mechanism for this may also be related to the inhibition of zinc absorption [37]. Many microorganisms require trace elements, such as iron and zinc, for survival and replication in the host and may increase in pathogenicity with supplementation [38]; thus, there is a concern about iron supplementation in malaria chemoprophylaxis programs. In general, iron (preferably with folate) should be administered to all pregnant women undergoing malaria chemoprophylaxis [39], much like the need for pyridoxine (B_6) supplementation during isoniazid treatment.

PARASITE INFECTION

The worldwide magnitude of parasite infection is enormous. One billion people are infected with soil-transmitted helminths (e.g., hookworms, *Ascaris,* and *Trichuris*), 200 million people are infected with schistosomes, and 400 million school-aged children are infected with various other intestinal parasites. Humans can host as many as 200 different types of parasites, and 1 worm can produce an average of 20,000 eggs per day. Intestinal parasites may be associated with a reduction in food intake, malabsorption, endogenous nutrient loss, and anemia. Although it is understood that parasites may lead to malnutrition, the extent to which malnutrition itself causes increased parasite infestation is not clearly known. Nonetheless, the conditions so frequently coexist that they need to be considered together [22].

The evidence demonstrating that parasites damage a child's health is unambiguous. Helminth infections in school-aged children are associated with cognitive deficits [40]. Several worm infections, including hookworm, schistosomes, and *Giardia,* are associated with iron-deficiency anemia and a significant loss of micronutrients. Blood loss can be as high as 45 mL/day, or the equivalent of 9.9 mg of iron [41]. Children free of parasites have better nutritional status, grow faster, learn more, and are freer of infections than are children with parasites.

PREGNANCY AND BREAST-FEEDING

Nutritional deficiencies associated with pregnancy may induce disturbances between the generation of free oxygen radicals and the production of antioxidants that scavenge free radicals, thus being associated with poor immune response to infection. This immune deficiency is partially made up for by breast-feeding.

Breast milk contains large quantities of secretory IgA, lysozyme-secreting macrophages, both T and B lymphocytes that release IFN-γ, migration inhibition factors, and monocyte chemotactic factors. All of these strengthen the intrinsic immune response. Thus, breast milk actively enhances the immune system via transfer of antibodies and lymphocytes.

Breast milk supplies the ideal mix, density, and physiological form of nutrients to promote adequate infant growth and development. It helps reduce exposure of infants to enteropathogens because of its antibacterial and antiviral properties and diminishes the risk of developing celiac disease. Breast milk may also have a similar effect on allergic, autoimmune, and inflammatory bowel diseases and certain tumors [42]. It protects against diarrhea, respiratory tract infections, otitis media, bacteremia, bacterial meningitis, botulism, urinary tract infections, and necrotizing enterocolitis and may improve overall vaccine response. There is enhanced protection for years after the termination of breast-feeding against pathogens such as *Haemophilus influenzae* type b and pneumococci, as well as the agents of otitis media, diarrhea, respiratory tract infections, and bronchitis [43].

As soon as breast-feeding is no longer adequate as the sole source of food, complementary feeding becomes imperative to avoid nutritional deficiency, particularly of iron. For children with normal birth weight born to a well-nourished mother, complementary feeding is required by age ~6 months. For children born to poorly nourished mothers, complementary feeding is required sooner, and low-birth-weight babies may need iron supplementation by as early as age 2 months, or their susceptibility to infection will be increased. In short, breast-feeding is the single best way to protect infants from infection.

HIV/AIDS AND NUTRITION

Malnutrition and nutritional alterations are common complications of HIV infection and play significant and independent roles in morbidity and mortality [44, 45]. The complex nature of AIDS wasting requires individualized strategies when providing nutritional support, and algorithms have been developed to assist in the diagnosis and treatment of malnutrition in patients with HIV infection [46].

AIDS studies initially documented weight loss and protein depletion associated with reduction in body cell mass in un-

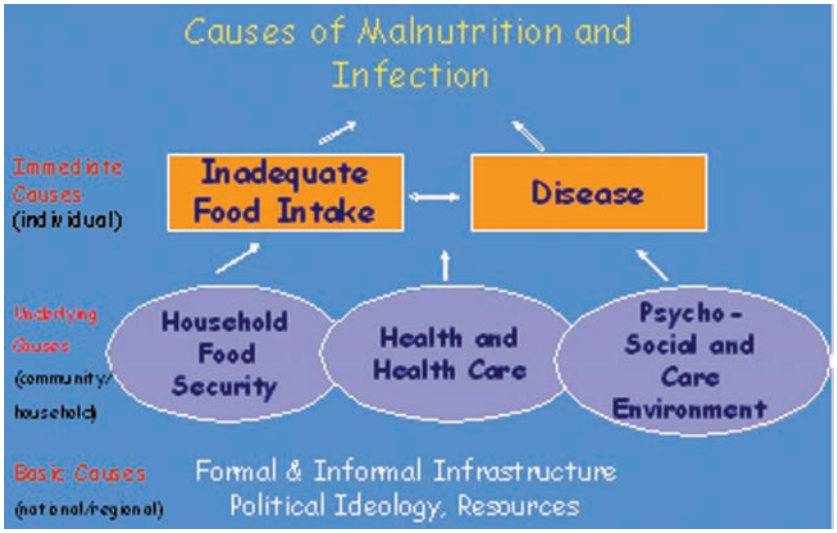

Figure 4. The multifactorial causes of malnutrition and infection

treated patients. HAART has led to a decreased incidence and prevalence of malnutrition. Nonetheless, altered body fat distribution and metabolic alterations, including hyperlipidemia and insulin resistance, may occur. The results of hypercaloric feeding studies, including the use of appetite stimulants, indicate that weight gain is predominantly fat. In contrast, anabolic agents and resistance training exercise have been shown to promote body cell mass repletion and skeletal muscle gain [47].

The development of malnutrition in HIV/AIDS is multifactoral and includes disorders of food intake, nutrient absorption, and intermediary metabolism. The effect of treating opportunistic infections that promote wasting was shown in a study of ganciclovir therapy for cytomegalovirus colitis, in which untreated patients experienced progressive wasting, whereas treated patients replenished body mass [48]. Total parenteral nutrition had a variable effect on body composition, with repletion occurring in patients with eating disorders or malabsorption syndromes and progressive depletion occurring in patients with serious systemic infections. Enteral nutrition also can increase body mass in patients with AIDS without severe malabsorption. Pharmacological appetite stimulation with drugs such as dronabinol also may lead to weight gain. The results of these studies indicate that nutritional support can improve nutritional status in properly selected patients with AIDS [49]. Nonetheless, there is also a downside, as the noted physician-anthropologist Paul Farmer has pointed out: treatment of persons living with HIV is just as important as are prevention measures [50], but this also takes a cohort of malnourished HIV-infected persons and moves them into the category of needing more nutrition, causing an even greater strain on marginal health care resources. Early assessment, attention to nutritional requirements, and prompt intervention can minimize wasting and replenish body cell mass [51].

THE FUTURE

The 21st century will bring better knowledge of the dynamics and kinetics of specific immune responses; discovery of and better understanding of newer cytokines in the control of nutritional status and immune activation; more real-time noninvasive sampling methods, such as saliva or urine tests for analysis, gene sequencing, and proteomics to examine individual susceptibilities; and improvements in mass vaccination. It may be possible to determine the specific mechanisms by which individual nutrients affect the immune system and thus to directly target activation and regulation of immune pathways.

Controlling malaria, measles, diarrhea, and parasitic infections can also help the body to absorb and retain essential vitamins and minerals. The estimated ratios of benefit to cost for such nutrition interventions range from 4:1 to 520:1 [52].

Children, who typically have less nutritional reserve than adults, are particularly susceptible to malnutrition and contaminated water. In addition to potability, water quality is also important for personal sanitation, to prevent contact spread of diarrhea and other infections. Currently, malnutrition is to blame for more than one-half of all deaths of children around the world, primarily deaths caused by diarrhea, pneumonia, malaria, and measles. Poor nourishment leaves children underweight, weakened, and vulnerable to fatal and nonfatal infections. It is estimated that feeding all children worldwide an adequate diet would prevent ~1 million deaths per year caused by pneumonia, 800,000 caused by diarrhea, 500,000 caused by malaria, and 250,000 caused by measles [7]. These conditions

are preventable, providing that the insight, coordination, political will, and funding are available.

Not all "functional" components of food with biological or protective activity have been identified, and we will not only identify new ones but also elaborate on their interactions with infection pathways. A question remains as to rising urban populations and the diminishing supply of both clean water and food. As water shortages grow, will desalination or recycling be economically feasible? Historically, food production expanded with population, but today, hunger and malnutrition are more the result of redistribution and politics than of production and natural disaster. Infection is inevitably tied to nutrition in both the developing and the developed world. With new technologies and political changes, it is hoped that a healthier, more disease-free, and better-nourished population will emerge.

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