23

Malnutrition and Host Defense

Susanna Cunningham-Rundles, PhD
Aeri Moon, MD
David F. McNeeley, MD, MPHTM

> *This at least I clearly know: that bread has different effects in the human body according as it is fine or coarse, made of wheat winnowed or unwinnowed, mixed with much or little water, kneed much or not at all, baked thoroughly or underbaked—and a thousand other differences besides. If one fails to consider these points or having considered does not understand them, how can he know anything about human disease?*
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> —Hippocrates, 460–377 BC,[1]

INTRODUCTION

The vital importance of nutrition in host defense has been recognized since the time of Hippocrates,[1] well before the appearance of the germ theory of infection in the nineteenth century.[2] Although traceable in origin to Metchnikoff[3] and the cell theory, immunology in its present form emerged in the 1960s,[4] when the morbidity of protein-calorie malnutrition (PCM) in children was also first characterized as a "thymolymphatic deficiency."[5] This concept is valid today.[6] Furthermore, there are indications that lesser degrees of perinatal nutrient insufficiency lead to reduced thymic function and reduced response to polysaccharide immunization in later life.[7,8] The central mechanism of nutrient interaction in the thymus involves zinc deficiency,[9,10] and this is directly associated with decreased host defense.[11] The effects of zinc deficiency are mediated by altered hematopoiesis and involve endocrine and neuroendocrine as well as immune mediators.[12] The selective sensitivity of the thymus to nutritional injury is specifically important to the formative phases of the fetal and neonatal immune system. Programmed involution of the thymus develops gradually over the first decades of life and has been viewed as the inevitable cause of human immune senescence.[13] Recent studies show that functionally active peripheral perivascular space thymic components predominate in adult life, and that regulatory alterations in neuroendocrine-thymus interactions rather than simple loss of thymic tissue mediate reduced T cell function.[13,14] Reduced zinc bioavailablity may be the key to loss of thymic function,[15] and supplementation may be effective in improving related immune responses.[16,17]

Innate immune signal transduction pathways are now appreciated as major regulators of adaptive immunity.[18] In the absence of memory T cells, neonates rely on the developing innate immune system. Recognition of microbes through common pathogen associated molecular patterns by the Toll-like receptor (TLR) system, begins at birth with colonization of the gastrointestinal tract and the priming of immune response through nutrient intake and bacterial cross talk.[19] The weaker response of neonatal monocytes and macrophages to multiple TLR ligands correlates with increased risk of infection.[20] Nutrients and growth factors present in human milk are critical regulators for the development of this system.[21,22] Nutrients also regulate functions of the complement system, and specialized natural killer (NK) cell receptors that distinguish "nonself," "missing-self," and "induced-self" and the TLR system.[23–25] Some edible plant products such as tea, mushrooms, and apples express alkylamines that are recognized by human gamma delta T cells as conserved molecular patterns shared by microbes and this can trigger immune response.[26]

Micronutrients have an important function in protection and restoration of cells and tissues after oxidant-mediated tissue injury, which normally occurs during host defense against infectious agents.[27] The cost of immune activation alone has been shown experimentally to have a measurable effect on survival.[28] Nutrient requirements for immune response or maintenance of host defense physiology may vary with stage of development, during the acute phase of infection or recovery from injury or surgical intervention. Glutamine, arginine, zinc, and vitamin A have been identified as conditional essential dietary nutrients or functional foods, required for immune recovery in selected settings.[29,30] Glutamine supplementation can reduce intestinal permeability and systemic infections in adults[31] and prevented sepsis when given before infection in a rat model of sepsis.[32] However, a trial of enteral supplementation to extremely low-birth-weight babies, who are glutamine deficient, did not reduce incidence of late onset sepsis or mortality.[33] More studies are needed to evaluate potential use in this setting.

Investigation of nutrient immune interaction is increasingly focused on genetic regulation.[34–36] Emerging studies show that genes regulating zinc metabolism affect signal transduction pathways especially those influencing immune response, responses to stress and redox imbalance, growth, and energy utilization.[37] The effects of nutrient level, deficiency or excess, on intestinal gene expression appear to correlate with disease expression as well as with changes in metabolism.[38,39] The discovery that host polymorphisms in the vitamin D receptor regulate immune response to mycobacteria and Hepatitis B[40,41] suggests that other host gene variants controlling nutrient metabolism may also affect response to endemic pathogens due to selection pressure. Dietary deprivation of a single nutrient can affect tissue expression of both genes directly associated with the deficiency and those regulating other nutrients that affect transport or redox balance as shown by the interaction of iron deficiency and copper genes.[39] Experimental malnutrition in the mouse illustrates the complexity of signaling effects. The early effect of multinutrient deprivation was to depress necrosis factor (NF) kappa B activity, which led to lower tumor necrosis factor-alpha (TNF-alpha) proinflammatory cytokine production and then to reduced levels of nitric oxide (NO). Low levels of NO then eliminated the negative feedback signal to NF kappa B activity leading to increased transcription activity in the later phase.[42] Knowledge concerning how nutrients can modify specific stages of the cytokine response program is relevant for the rational design of future supplementation trials.

The effect of malnutrition on clinical infection is to increase severity and morbidity.[43] The mechanisms include both modulation of specific cytokine responses and the overall cytokine pattern. Malnutrition is associated with impaired cytokine response to antigen[44] and increased levels of circulating proinflammatory cytokines.[45] The acute phase response to infection is blunted in malnutrition.[46] Infection in chronically malnourished children is associated with an increased cortisol response and greater loss of amino acids.[47] Concurrent infection also complicates the evaluation of malnutrition since transient losses of micronutrients may mimic a true deficiency.[48] Infants appear to have an intrinsically weaker ability to produce a compensatory anti-inflammatory response and therefore may be especially sensitive to the combination of infections and nutrient deficiency.[49] Some of the observed effects of malnutrition involve reactivation of opportunistic

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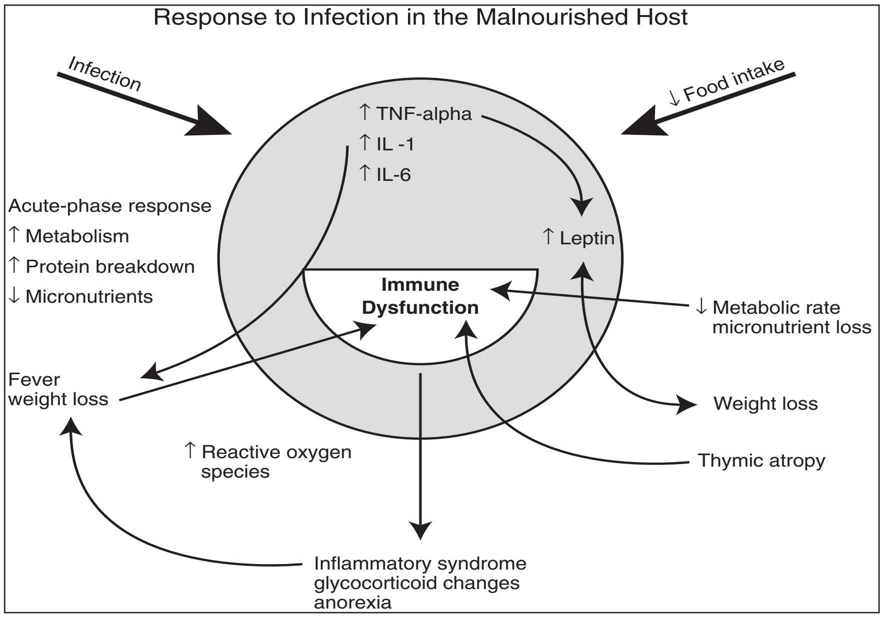

Figure 1 Illustrates some of the key interactions that lead to altered immune response in the malnourished host during infectious exposure. IL = intereleukin; TNF = tumor necrosis factor.

infections leading to altered activation of the acute phase response as illustrated in Figure 1. Examples include the effects of malnutrition on chronic infections such as *Mycobacterium tuberculosis* (TB), the human immunodeficiency virus type 1 (HIV-1) infection, and hepatitis.[41,50–53] Nutrients can have direct actions on specific immune cells and pathways or affect many different types of cells[54] (see Figure 2). Mechanisms of nutrient action may vary according to setting, concentration, and valid assessment requires appropriate methodology.[55–57] The impact of supplementation is also affected by conditions in the host.[58] Correlations that are observed in the compromised host may not hold true in the healthy host.

PCM nutrient deficiency occurring in children in the absence of contributing clinical cause is usually the result of poverty, lack of adequate supply, or other environmental factors.[59] Rare innate occurrences include the genetic defect of zinc metabolism, Acrodermatitis enteropathica (AE),[60] and defects of copper in Menkes or Wilson's disease.[61] However, deficient intake of essential nutrient requirements may easily be caused by altered metabolism in association with an underlying congenital condition, or acute illness and this impairs or worsens host response to emergent pathogens. Although malnutrition is often considered as mainly an issue for underdeveloped countries, suboptimal nutrition is common in children throughout the world, and is a significant cause of susceptibility to infection.[62] The changing social conditions of childhood, increasingly fragmented family life, and global infections have shifted the responsibility for children's health to the community. Professional knowledge of how nutrients may affect the development of immune response will have greater critical importance for preventive efforts to support future host defense against both old and emerging new pathogens.

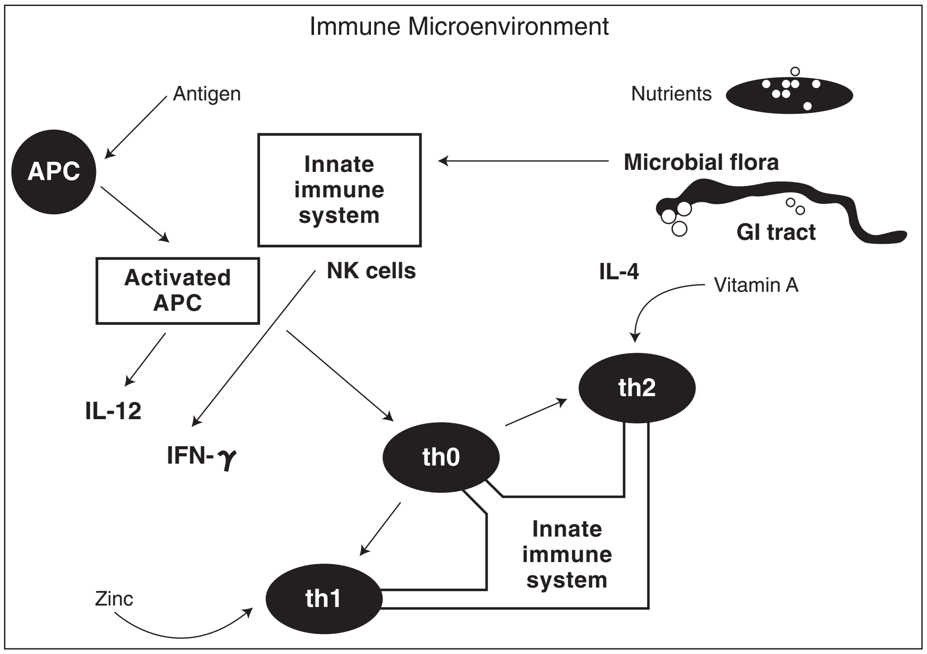

Figure 2 Indicates the role of nutrients in how the microenvironment influences the production of cytokines by the adaptive immune system. APC = antigen-presenting cell; GI = gastrointestinal; IFN = interferon; IL = interleukin; NK = natural killer; Th = T helper.

THE MICROENVIRONMENT AND MUCOSAL IMMUNE RESPONSE

The effect of nutrients on host response is pathogen specific and is affected by site of action, for example, the gastrointestinal associated lymphoid tract (GALT), thymus, spleen, regional lymph nodes, or immune cells of the circulating blood and upon the presence of infection or other immunogens. Thus experimental zinc deficiency in human volunteers decreased T-helper type 1 (Th1) production of Interleukin-2 (IL-2) and interferon gamma (IFN gamma), but had no effect on IL-4 response of peripheral blood mononuclear cells.[9] In contrast, zinc deficiency in nematode infected mice caused enhanced parasite survival in association with decreased T-helper type 2 (Th2) IL-4 responses in the GALT.[63] Differentiation of immune cell function and cell–cell interactions are critically determined by the local immune microenvironment and the presence of specialized immune cells, which may be tissue specific such as the adaptive intraepithelial lymphocytes in the intestinal tract, products such as mucus, and soluble mediators such as cytokines, interferons, lysozymes, and defensins. Studies in a mouse model of visceral leishmaniasis have shown that malnutrition promoted visceralization through loss of lymph node barrier function after *Leishmania donovani* infection. This was caused by excessive production of prostaglandin E_2, decreased levels of IL-10 and NO.[64] The effect of diet on mucosal integrity is a key measure of effective nutritional rehabilitation in infants. Protein deficiency predisposes both to skin and mucosal atrophy and compromises barrier function. As shown by a comparative study of maize-soy-egg to the standard milk diet in the treatment of kwashiorkor, milk had a better effect on reducing intestinal permeability as shown by the lactulose–rhamnose test. Despite the greater frequency of diarrhea, milk treatment was associated with reduced sepsis and improved survival.[65]

Chemotaxis, phagocytosis, and microbial killing mechanisms become impaired in malnutrition causing susceptibility to infections. The mechanisms involve reduced production of key mediators including complement C3, leukotrienes, cathelicidin antimicrobial peptide, and leptin.[66–69] The activities of many innate immune cells including neutrophils, monocytes, macrophages, dendritic, and NK cells are susceptible to altered nutrient levels.[70–72] Deficiencies can be particularly critical in the perinatal period as shown by

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the reduced level of NK cells in neonates born to mothers who were selenium deficient and the therapeutic effect of short-term renutrition in malnourished infants on defective neutrophil phagocytic activity.[73,74]

Vitamin A and vitamin D are critical regulators of mucosal immune function. Experimental vitamin A deficiency leads to functional disturbance of intestinal epithelium enzymes, diarrhea, and increased bacterial translocation in gnotobiotic rats.[75] Supplementation of vitamin A deficient measles patients lowered the risk of measles-related pneumonia.[76] In a study of vitamin A supplemented children infected with enteropathogenic *Escherichia coli* investigators observed reduced monocyte chemoattractant protein –1 levels compared with children in the placebo group consistent with an anti-inflammatory effect.[77] A recent study in mildly malnourished uninfected children, using the lactulose/mannitol test reported that intestinal barrier function was inversely correlated with serum retinol concentrations.[78] Retinoic acid, the vitamin A metabolite, is an inducer for the gut-homing specificity of T cells that enhances the expression of the integrin alpha4beta7 and CCR9 on T cells upon activation.[79] Retinoic acid has also been shown to synergize with GALT-DC-derived IL-6 or IL-5 to induce IgA secretion.[80] Since impaired gut immune response in early infancy may contribute to the development of atopic sensitization, Pesonen and colleagues looked for an association between plasma retinol concentrations and the subsequent development of allergic symptoms in healthy infants. They found that retinol concentration at 2 months correlated inversely with positive skin prick test at 5 and 20 years, and with allergic symptoms at 20 years.[81]

Both experimental vitamin D deficiency and human vitamin D receptor polymorphisms are associated with inflammatory bowel disease.[82,83] Association between subclinical vitamin D deficiency and lower respiratory tract infections in young children has also been reported.[84] Reduced vitamin D status is associated with susceptibility to active *M. tuberculosis* infection. Recent studies have shown that TLR stimulation of human macrophages induces vitamin D-1-hydroxylase genes, leading to the conversion of 25(OH) D3 to active 1,25(OH) 2D3, expression of the vitamin D receptor, and leads to antimicrobial peptide gene expression, induction of cathelicidin, and killing of intracellular *M. tuberculosis*.[85] This mechanism is also important for resistance to *Pseudomonas aeruginosa*, an important pathogen in cystic fibrosis.[68,85]

Dietary nucleotides provide preformed purine and pyrimidine bases that can be used for nucleic acid synthesis and may provide a means to support growth of the gut in the premature infant through reduction of intestinal permeability and absorption of macromolecules by enhancing immune response.[86,87] Martinez-Augustin and colleagues have shown that IgG antibodies against the main antigenic proteins in cow's milk are generally higher when nucleotide supplementation is provided. This difference reached significance for antibody to beta-lactoglobulin at 30 days of life when gut closure had occurred.[88] Others have shown that supplementation enhanced infants' responses to polio vaccination[87] and that the immunophenotype of infants fed nucleotide supplemented formula tended to be more like those fed human milk.[86] A recent study has reported that formula-fed infants given nucleotide supplementation had significantly higher responses to tetanus toxoid compared to controls.[89] Others have speculated that the benefits of nucleotides on the gastrointestinal and immune systems in the premature infant are related to increased splanchnic blood flow and effects on gut-associated lymphoid tissues.[90]

Human milk provides bioavailable micronutrients such as zinc, cytokines, and growth factors that are important for development of the gastrointestinal tract, as well as a source of maternal antibodies for passive protection against microbes common to mother and infant.[91] Secretory IgA antibodies in milk reactive against antigens in the maternal gut are protective against gastrointestinal disease.[92] In addition, milk contains oligosaccharides and glycans that inhibit binding by specific enteric pathogens.[93] IgA antibodies in colostrum and human milk may also prevent antigen entry at the intestinal surface of the breast-fed infant. A low IgA content in maternal milk is associated with development of cow's milk allergy suggesting that low IgA in milk is associated with defective exclusion of food antigens.[94] The composition of milk differs in mothers of premature infants from those from mothers of full-term infants. Higher concentrations of epidermal growth factor and transforming growth factor-alpha which are trophic peptides that support recovery of injured gastrointestinal mucosa have been found in milk from mothers with extremely preterm babies.[95]

Maternal malnutrition is associated with decline in total milk IgA, C3, and C4 and lower thymic weight in infants.[96] Perinatal supplementation of malnourished mothers with vitamin A leads to higher levels in milk postpartum and decreased infections and morbidity in infants in the perinatal period.[97] Low levels of fatty acids, such as decosahexanoic acid in maternal milk correlate directly with low levels in malnourished children. Recent studies show that bioactive immune mediators in milk such as transforming growth factor-beta and soluble CD14 receptor (sCD14), the bacterial pattern recognition receptor, are key elements in regulating the development of neonatal immunity. Mammary epithelial cells produce sCD14 in response to lipopolysaccharide (LPS) or bacteria, which activates intestinal epithelial cell secretion of IL-8, TNF-alpha, and epithelial neutrophil activator.[98] Another study showed that supplementation with fish oil during pregnancy leads to increased omega-3 polyunsaturated fatty acid levels that correlate with increased IgA and sCD14 levels, suggesting a possible fundamental relationship between fatty acid status and mucosal immune function.[99]

HOST DEFENSE IN PROTEIN-CALORIE MALNUTRITION

PCM, sometimes termed protein-energy malnutrition, is the most common cause of secondary immune deficiency in the world because of wide spread chronic and seasonal food shortages, as well as chronic poverty, the deprivations of war, and maternal malnutrition.[100] PCM may involve energy deficiency, protein deficiency, and vitamin and mineral deprivation. If prolonged, PCM produces wasting and stunting. Protein insufficiency alone, with or without infection, causes edema associated with hepatomegaly from fatty infiltration of the liver. The clinical manifestations are related to type, severity, and duration of nutritional impairment and may be subclinical, reversible, or irreversible depending upon availability of treatment, presence of other diseases or complicating disorders, and the degree of damage. Classically, PCM is divided into two types—marasmus and kwashiorkor. Marasmus is caused by total calorie deficiency, and is characterized by chronic wasting and gross underweight. Kwashiorkor develops due to protein deficiency in the diet and causes moderate growth retardation. Children with kwashiorkor have a characteristic moon facies and altered hair and sad appearance.[59] Vitamin and mineral deficiencies are commonly found in both marasmus and kwashiorkor. The causes of protein deficiency include use of low-protein milk substitutes such as rice "milk," which contains no milk product and other substitute beverages.[101–103]

Malnutrition can be classified as either primary or secondary. Primary malnutrition is caused by inadequate calorie and nutrient intake. Although calorie intake is presumed to be adequate in developed countries, inadequate intake of micronutrients including vitamin A, E, calcium, iron, and zinc are actually fairly common among children under 10 years of age although often goes unrecognized especially in minority populations.[104] Primary malnutrition in infants can also occur through child neglect or accidental nutrient insufficiency.[105,106] Rarer causes of single nutrient deficiency include a primary genetic defect in the mother that impairs zinc transport from blood into breast milk and leads to secondary zinc deficiency in infancy[107] and inheritance of the autosomal recessive zinc transporter mutation AE in the infant.[108]

Primary malnutrition is associated with atrophy of lymphoid organs and profound immune malfunction leading to susceptibility to pathogens, reactivation of viral infections, and development of opportunistic infections. Malnutrition in the neonatal period and early childhood can lead to severe immune deficiency and high mortality. Although the effects can be broad, impaired T-cell responses secondary to effects on thymic architecture and function are the most common. The thymus is central to the development of controlled adaptive immunity in providing the microenvironment in which bone-marrow-derived progenitors undergo proliferation, T-cell

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receptor rearrangement, and thymocyte differentiation into mature T cells.[109] Congenital thymic absence, DiGeorge syndrome, is associated with recurrent infections, which can be fatal. Other developmental anomalies that stem from chromosome 22q11 deletions comprising the CATCH-22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia) group of disorders may also have clinically significant immune deficiency in association with reduced thymic function.[110] A zinc finger gene, *ZNF74*, has been identified in the commonly deleted region.[111] Nutritionally caused thymic involution is very similar to congenital thymic aplasia in terms of effects on immune function and host defense. Measurements of thymic size and the frequency of T-cell receptor excision circles indicate that both thymus size and function are sensitive to perinatal malnutrition.[8] A small thymus at birth in infants born in impoverished environment predicts an increase in risk of infection related mortality in infancy.[112] Seasonal variations in breast milk associated with food shortages leading to reduced levels of IL-7 is a possible mediator of these effects.[8]

Thymic atrophy caused by PCM is associated with hormonal imbalance, loss of leptin, and increase in serum glucocorticoid level. Leptin levels normally increase acutely during infection and inflammation,[113] but this does not occur in PCM. The reduction of serum leptin levels and insulin-like growth factor-1 in marasmus and kwashiorkor[114] may compromise response to infection. Loss of immune function in malnourished children correlates with low leptin levels, and refeeding leads to increase in leptin levels and immunological recovery.[115] Immune structure and function are more compromised in edematous PCM than in nonedematous PCM. Children who are malnourished mount a partial acute phase response to infection and this defect is more marked in children with kwashiorkor, the edematous form of PCM.[116] Differences have been observed at the level of specific protein pools suggesting that in kwashiorkor expansion of the haptoglobin pool was due to reduction in the rate of catabolism relative to the rate of synthesis. Infections are commonly found. For children living in a rural environment in a developed country, one study reported that one-third of all patients hospitalized for malnutrition had bacterial infections.[117] Host response to infection is also altered. Well-nourished children show a relative increase in B lymphocytes in response to bacterial infection, while B cell response was significantly reduced in malnourished children.[118] In general the humoral immune response is relatively preserved, although serum levels of IgA1, IgA2, and C4 tend to be higher than in normal children, serum level of C3 and the proportion of B cells are significantly lower.[119] IgE levels are lower even among asthmatic children.[120] Although response to vaccines is often effective,[121] there is reason for caution as relatively few studies have examined the potential long-term effects of neonatal nutrient deficiency.

Nutrient deficiencies may have an indelible effect during critical periods of early development by exerting an imprinting effect on the fundamental program of future development. This concept, advanced by Barker as "developmental origins of health and disease" hypothesis,[122] has been applied to nutritional status at birth by Dobbing[123] and to immune response.[7,124] Mc Dade and colleagues reported that adolescents who were small for gestational age at birth had lower thymopoietin levels when compared with adolescents who were appropriate for gestational age at birth. In both groups thymopoietin level during adolescence correlated with growth in length during the first year of life. In addition, the probability of mounting a positive antibody response for adolescents who were small for gestational age and also undernourished at the time of immunization was lower compared to adolescents who were appropriate for gestational age.[124] Moore and colleagues have reported similar findings in adults using the same purified Vi surface polysaccharide extracted from *Salmonella typhi*. Interestingly while they found a correlation for both IgG and IgM antibody response to Vi vaccine with birth weight, they did not find this for rabies or typhoid. The studies suggest that polysaccharide T independent immune response may be specifically compromised by fetal growth retardation.[8]

Secondary malnutrition can be caused by reduced intake of food, malabsorption, impaired nutrient utilization, and nutrient losses associated with chronic infection and many other clinical conditions as well. Examples include inflammatory bowel disorders, celiac disease, chronic anemia, renal disorders, and cystic fibrosis. In both primary and secondary malnutrition, understanding of the relevant genetic mechanisms can be helpful in approaching the clinical manifestations. Genetic mechanisms of malnutrition that affect susceptibility to infectious disease include mutations affecting metabolism of the trace elements zinc, iron, and copper, and several vitamins as well as those underlying complex, inherited disorders such as cystic fibrosis and celiac disease. Primary malnutrition impairs immunity impeding host response to infection, but these effects are reversible with nutrient repletion. However, calorie and nutritional supplement alone cannot resolve the secondary malnutrition with organic etiology.

Obesity is emerging as a malnutrition syndrome that develops when energy intake exceeds expenditure. Human obesity often becomes a permanent condition and appears to involve changes in the neural-endocrine network that regulates energy intake, expenditure, and storage[125] Leptin, the adipocyte-secreted hormone that regulates weight centrally and ghrelin, a gastrointestinal hormone regulating feeding and energy balance, are signals in this system. Leptin has cytokine-like activities and acts as a mediator for the interactions of nutritional status with neuroendocrine and immune responses. Leptin production increases acutely during infection perhaps in response to glucocorticoids and is higher in survivors of sepsis.[125,126] Leptin deficient mice show increased mortality from bacterial infections.[69] Congenital human leptin deficiency is a rare cause of severe early-onset obesity characterized by absence of leptin and carries a high risk of death due to infection in childhood.[127,128]

Obesity-prone individuals appear to have an inborn reduction in their catabolic responses to glucose, leptin, and insulin.[128,129] Elevated circulating leptin levels are characteristic in obesity and may contribute significantly to the reported low-grade systemic inflammation[128] and perhaps to the high incidence of atopy.[130] Generally the incidence and severity of specific types of infectious illnesses are higher in obese persons.[131] Weight loss in obesity is associated with improved immune function in vitro.[132] The genetic interactions between leptin and its receptor are affected by host polymorphisms, some of which are associated with increased BMI and may promote the immune dysfunction associated with obesity and risk of non-Hodgkin lymphoma as recently proposed.[133] A Common inherited IL-6 promoter polymorphism has been linked to increased serum leptin and increased BMI suggesting a functional relationship since IL-6 which increases acutely in infection also reduces fat mass.[134] Obesity may also involve altered metabolism secondary to changes in microflora. The gut microbiota as a whole is essential for production of short chain fatty acids from polysaccharides, and is a regulator of host metabolism through direct effects on fat storage.[135] A direct role for viral infection in obesity has also been proposed[136] and may operate through some of these mechanisms.

MICRONUTRIENTS AND IMMUNE FUNCTION

Selective micronutrient deficiencies can occur when food and calorie intake is adequate. Iron, copper, and zinc deficiencies are the most common. Results from a large double blind trial of fortified milk in preschool children showed that intervention was associated with reduced morbidity from diarrhea, respiratory infections, and other illnesses, as well as improved iron status and growth.[137] Selenium deficiency occurs in environments where selenium levels are low in the soil or where bioavailability is limited. As a constituent of selenoproteins, selenium is needed for the functioning of neutrophils, macrophages, NK cells, and T lymphocytes. Mild selenium deficiency is relatively widespread and appears to worsen viral infection.[138] Selenium and vitamin E deficiency in the mouse have been shown to promote the virulence of Coxsackie B3 virus and influenza by inducing genetic changes in the genomes of the viruses.[139] Selective micronutrient deficiency frequently occurs in patients with underlying systemic illnesses, chronic viral infection, and in low-birth-weight infants.[140,141] Low dietary intake of antioxidant nutrients can influence both response to infection or produce an inflammatory state that mimics infection. Nair

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Table 1 Regulatory Effects of Micronutrients on Immune Response

Nutrient	Target cell	Effect	Mechanism
Zinc	T cell, NK cell, B cell	• Deficiency promotes infection, impairs immune response, ↓ hematopoiesis • Lymphopenia, dermatitis, enteritis • ↓ Thymic activity • ↓ Antioxidant enzyme activity	• Deficiency causes glucocorticoid mediated early T cell and B cell apoptosis • Required for thymic hormone function • Required for activity of >100 enzymes • Required for zinc finger dependent transcription factors
Iron	T cell, monocyte	• Iron deficiency causes ↓ neutrophil oxidative burst activity and ↓IgG4 levels • Anemia linked with mortality in HIV Iron excess causes infection in the genetically susceptible host	• Promotes Th-2 response, ROS production needed for intracellular killing; chronic ROS linked to immune dysfunction • Promotes bacterial growth, enhances HIV viral replication • Host polymorphisms, *HFE* gene affect regulate iron
Copper	Monocyte, T cell, neutrophil	• Deficiency leads to infections • Deficiency ↓ proliferation, phagocyte activity	• Modulation of MHC Class II expression • Affects selenoglutathione peroxidase activity • Reduces IL-2 response
Selenium	Monocyte	• Deficiency suppresses antigen presentation • Repletion ↑proliferation • Deficiency linked to ↑ HIV infection	• Antioxidant • Affects IL-2 response, regulates NF kappa B • May interact with viral genes
Vitamin A	T cell, NK cell, B cell	• Deficiency causes infections, mortality from infections, ↓ NK activity • Repletion improves gut integrity at weaning • Repletion reduces morbidity, mortality from infections	• Promotes Th-2 cytokine and IgA production • Inducer for gut-homing of T cells • IL-2 receptor beta, interferon regulatory factor, transcription factor mRNA • Affects IL-12 and IL-10 production
Vitamin C	Phagocyte	• Promotes phagocytic and NK activity • Reduces stress IL-6 response • Improves response to strep infection • Reduces growth of *Helicobacter pylori*	• Decreases monocyte response to LPS • Increases phagocytosis • Increases NK activity
Vitamin D, 1,25-dihydroxy-vitamin D3	T cell, B cell, monocyte, macrophage, dendritic cell	• Vitamin D3 affects differentiation, maturation, and function of cells	• Functions through a nuclear receptor, vitamin D receptor (VDR) which binds to response elements in target genes
		• Vitamin D3 suppresses autoimmune disease in animal models • Vitamin D deficiency promoted TB infection	• Affects differentiation of monocytes, dendritic cells • VDR polymorphisms regulate response to mycobacteria, hepatitis B, inflammatory bowel disease through TLR signaling
Vitamin E	T cell, B cell, monocyte	• ↑ Proliferative, IL-2 response in vitro • Improves skin test response • Deficiency may promote viral virulence	• Modulates cyclic AMP response element binding proteins • Affects prostaglandin production

and colleagues[142] observed that patients with gastritis had reduced alpha-tocopherol levels in serum and mucosa irrespective of *Helicobacter pylori* infections, whereas carotenoids and ascorbic acid levels were similar to controls. Inflammation induced by *H. pylori* infection, especially with the CagA positive strain, is associated with decreased gastric vitamin C into the gastric lumen in children.[143] Studies in mice show that vitamin C and the carotenoid, astaxanthin, show antimicrobial activity against *H. pylori* that appeared to be mediated by altered immune response characterized by a shift from a Th-1 type immune response to a mixed Th-1/ Th-2 response, which was dominated by IL-4 and IFN-gamma production.[144] Strains of *H. pylori* that were rendered more sensitive to antioxidants were less able to colonize the gastric mucosa suggesting that both antioxidant as well as immune mediated effects could be significant.[145]

Trace elements and vitamins perform antioxidant functions through participation in enzyme-catalyzed reactions. These reactions are essential to offset potential oxidative damage caused by free radical formation. Three antioxidant enzymes, the copper, zinc, and manganese superoxide dismutases, require trace metals for biological activity. In addition, micronutrients are pivotal regulators of cytokine production. Intracellular redox balance has a signaling role in immune cell development and function and the antioxidant effects of micronutrients regulate cytokine production.[146] Table 1 summarizes the role of key micronutrients in regulation of immune response. The implications and significance of these functions for the development of immune response to pathogens are outlined below:

Iron

The controversy about iron supplementation has continued over several decades because of concern that excess, or inappropriate timing of iron repletion, would promote bacterial growth. The current consensus is that iron supplementation has a high probability of adversely affecting outcome in individuals who present with concurrent infection or who carry genes predisposing to iron overload.[147] Iron overload secondary to blood transfusion is a serious complication of beta thalassemia that increases both risk and severity of infection.[148,149] Circulating levels of micronutrients (vitamins A and E, zinc, selenium, and copper) are lower in children with thalassemia maintained by red cell transfusion compared to age matched controls.[150] In hereditary hemochromatosis, a disorder of increased iron uptake, there is a paradoxical iron deficiency of macrophages, which may actually result in increased resistance to bacterial pathogens.[151] Iron chelation therapy in *Plasmodium falciparum* infection alleviates the clinical course of cerebral malaria in children. However, the basis of this appears to be enhanced generation of NO rather than reduced iron availability to the parasite.[152]

Iron deficiency anemia in children is associated with reduced neutrophil oxidative bust activity and reduced levels of IgG4.[70] Iron supplementation has a significant and positive effect on iron status in anemia secondary to malaria and no impact on the incidence of malarial infection.[153] Vegetarian diet and *H. pylori* infection can be causes of iron deficiency anemia.[154,155] Pangastritis is more common in children whose *H. pylori* infection is accompanied by anemia.[143] Experimental iron deficiency leads to upregulation of apical iron transport-related proteins, transferrin receptor and heme oxygenase, and copper loading genes, and decreased expression of genes involved in the oxidative stress response.[39]

Zinc

Zinc deficiency affects about one-third of the world's populations and is a frequent complication of PCM.[156] Zinc deficiency is also a significant complication of IgA deficiency, fetal alcohol syndrome, sickle cell disease, enteritis, celiac disease, and many forms of diarrhea.[7,157,158] Zinc deficiency presenting as dermatitis similar to AE can be a sign of cystic fibrosis.[159] Zinc is an essential cofactor for the activity of many enzymes including thymic hormone.[10] Deficiency leads to reduced Th-1 cytokines and thymic hormone activity[11,160,161] and to lymphopenia.[162] Zinc supplementation improves host defense in severely malnourished children.[163] Prolonged deficiency causes reprogramming of the immune system, beginning with activation of the HPA (hypothalamic pituitary axis) causing chronic production of glucocorticoids that accelerates apoptosis among early T and B cells.[12] Zinc deficiency induced in human volunteers led to decreased IFN-gamma and IL-2 production but not IL-4, IL-6, or IL-10.[9] Zinc inhibits LPS-induced TNF-alpha and IL-1-beta release from primary human monocytes by inhibiting the enzyme activity of phosphodiesterase leading to increasing intracellular cycic GPM (cGMP) (guanosine 3',5'-cyclic monophosphate) levels.[164] A recent study suggests that the enhancing effect of zinc on Th-1, cytokine response in cultured human peripheral blood cells, is mediated by NK cell upregulation and increased IFN-gamma production.[165] The implications for enhancement of immune response, for example, to vaccine, may be complex as shown by a recent study of response in children to subunit B cholera toxin. Although zinc supplementation enhanced vibriocidal antibody response, cholera toxin response was suppressed.[166]

The autosomal recessive genetic defect of zinc absorption, AE, presents in infancy as skin lesions, diarrhea, alopecia, and increased incidence of infections caused by severe immune deficiency.[60] Immune defects in AE range from severe thymic atrophy and profound lymphopenia to skin test anergy and loss of NK cell activity.[11] AE is centrally caused by mutations in SLC39A4, which encodes a ZIP zinc transporter protein. Increased zinc availability increases expression of zinc transporters and therefore patients with AE respond to increased zinc supplementation.[167] Differential mRNA display and cDNA array analysis have identified zinc-regulated genes. Dietary zinc intake, high or low, affected about 5% of genes in the monocytic/macrophage THP-1 cell line. Many needed for host defense were among those identified as zinc responsive, including cytokine receptor genes and genes associated with amplification of the Th1 immune response.[168] A recent study examined the effect of modest zinc supplementation in healthy volunteers on immune function. TNF-alpha and IL-1-beta expression were greater in activated monocytes and granulocytes, and IFN-gamma mRNA levels were higher in activated T lymphocytes compared to baseline.[169] Zinc-fortified formulas have been used to improve both linear growth and immunocompetence as shown by improved delayed type hypersensitivity, enhanced lymphoproliferative responses, and increased salivary IgA in severely malnourished infants.[170]

Copper

Copper and zinc deficiencies are common in children with hypoproteinemia and anemia and this leads to reduced antioxidant function as measured by Cu/Zn superoxide dismutase (SOD-1) activity.[171] Transgenic mice overexpressing SOD-1 demonstrate a significant increase in macrophage release of TNF-alpha and the metalloproteinases.[172] Zinc competes with copper for gastrointestinal uptake, and increased zinc intake can induce copper deficiency causing clinically significant neutropenia.[173] The IL-2 response is reduced in copper deficiency[174] and marginal copper deficiency may lead to immune dysfunction.[175] Serum copper or ceruloplasmin levels reflect the severity of malnutrition.[176]

Copper also interacts with iron since ceruloplasmin, which contains most of the plasma copper, is a ferroxidase. Ceruloplasmin facilitates release of tissue iron into plasma by oxidizing ferrous iron into ferric iron, which is then bound to transferrin for delivery to the bone marrow for hematopoiesis. Aceruloplasminemia is an inherited disorder of iron metabolism.[177] Copper transporting P-type ATPases, ATP7A, and ATP7B, maintain copper balance. Impaired intestinal transport of copper, resulting from mutations in the *ATP7A* gene, leads to Menkes disease. Defects in a similar gene, the copper transporting ATPase *ATP7B*, result in Wilson disease. This ATP7B transporter has two functions: transport of copper into the plasma protein ceruloplasmin, and elimination of copper through the bile.[178]

Selenium

Selenium is an important micronutrient for health[179] and is critical for antioxidant function acting via the selenium-dependent enzyme, glutathione peroxidase, to protect cellular membranes and organelles from peroxidative damage. Soil deficiencies of selenium and iodine are common in some countries such as New Zealand, Australia, Finland, and in parts of China.[180] Selenium deficiency can be a critical component of PCM and is linked with congestive heart failure in this setting.[181] Juvenile cardiomyopathy (Keshan) appears to involve both selenium deficiency and enteroviral infection. Experimental studies suggest that selenium deficiency enhances viral virulence.[182] Selenium has been used in vitro to correct membrane fluidity, IL-2 production, and IL-2R expression in patients with chronic hepatitis, which were significantly lower than controls.[53] Some studies have suggested that risk of cancer is increased in selenium deficiency.[183,184] Selenoproteins are an important component of the antioxidant host defense system affecting leukocyte and NK cell function.[185] Selenium is emerging as a critical micronutrient in host defense against viral infection since selenium deficiency is associated with progression in HIV disease and in viral shedding.[186,187]

Antioxidant Vitamins

The antioxidant vitamins, vitamin E, C, A, and the precursor of vitamin A, beta-carotene, are cofactors in immune response. Vitamin A (retinol) is a key micronutrient needed for resolution of infection. In environments with endemic low levels of vitamin A, supplementation significantly reduces childhood mortality.[188] Vitamin A has long been appreciated as a significant factor in the severity of infection such as measles, rotavirus diarrhea, and HIV in the malnourished host.[189,190] Reduced levels of serum trans-retinol are common in infants of HIV-1 infected mothers.[191] Xerophthalmia is associated with childhood infections such as measles, diarrhea, and respiratory tract infections among hospitalized children.[192] Respiratory infection and diarrhea can be signs of subclinical low levels of vitamin A.[193] Serum retinol and provitamin-A as well as carotenoid concentrations are lower in children with acute phase infections compared to healthy controls and correlate inversely with C-reactive protein suggesting decreased synthesis or increased utilization of these antioxidants in infection.[194] Low vitamin A levels are associated with the occurrence of chronic bacterial infections and splenomegaly as well as high neopterin levels in common variable immune deficiency or hypogammaglobulinemia.[195] Supplementation in vivo led to improved immune function in vitro.

Vitamin A deficiency impairs both Th1 and Th2 mediated immune responses, although Th2 responses seem to be principally affected.[196] Vitamin A deficiency at the time of antigen exposure induces secretion of T regulatory IL-10 and diminishes Th-1 memory cell response in the mouse.[197] Organized vitamin A supplementation in areas of endemic deficiency is beneficial for protection against diarrhea and acute respiratory infections.[198] The mechanism of vitamin A protection against morbidity of infections has not been clarified. To address this issue, a large study of children less than 2 years of age were followed in randomized, double-blind, placebo-controlled, vitamin A supplementation trial and IL-4, IL-6, IFN-gamma, and gastrointestinal pathogens were evaluated in stool. Vitamin A-supplemented children infected with enteropathogenic *E. coli* had reduced IL-4 and IFN-gamma levels but increased IL-4 levels when infected with *Ascaris lumbricoides*. IL-4 levels increased and IFN-gamma levels decreased among vitamin A-supplemented children with diarrhea compared with the placebo group. These findings suggest that the effects of vitamin A may depend on the infecting enteric pathogen and clinical stage.[199]

Vitamin E is a strong antioxidant that can support monocyte/macrophage-mediated response.[200,201] Vitamin E influences T cell function by down modulating prostaglandin E_2 in elderly subjects.[202] Current studies suggest that vitamin E deficiency may enhance virulence in viral infections.[139] Vitamin E supplementation enhances proliferative response in vitro[203] and improves IL-2 cytokine response.[204] Vitamin E deficiency causes reduced transferrin receptor internalization in the mouse, which suggests restriction of intracellular iron stores that would be needed for cellular function and proliferation.[205] A recent study has shown that antioxidant deficiency is common in a very large cohort of cystic fibrosis patients. Carotenoid and vitamin E deficiencies were found to occur early in the course of the disease and level of antioxidants decreased with bronchial infection.[206]

Vitamin C is a regulator of redox and metabolic checkpoints controlling activation and survival of immune cells. In vitro studies have shown that vitamin C selectively influences cytokine production in response to LPS by reducing the number of monocytes producing IL-6 and IL-2 without affecting IL-1 and IL-8.[207] Ascorbate regulates the phagocytic process by decreasing free radical production and thus potentially reduces the severity of the endotoxin response.[208] During stress exercise, contracting skeletal muscle is a major contributor to the exercise-induced increase of plasma IL-6; supplementation with vitamins C and E attenuates this response.[209] Vitamin C concentrations in the plasma and leukocytes decline during infections and stress. Supplementation with antioxidant vitamins including vitamin C has been shown to improve immune response to group A streptococcal infection compared to penicillin alone.[210] Supplementation may enhance phagocytosis and NK cell activity,[211] *H. pylori* infection is associated with a decrease in gastric juice ascorbic acid concentration; this effect is greater in children infected with the CagA-positive strain A.[143] Both vitamin C and astaxanthin, a carotenoid, show antimicrobial activity against *H. pylori* that may be mediated through immune mechanisms.[212]

MALNUTRITION AND CHRONIC INFECTION

Chronic infection commonly involves malabsorption and malnutrition that is associated with altered cytokine patterns affecting both regional and systemic immune response altering metabolism and growth. Although less prevalent in industrialized countries, chronic infections such as HIV and *M. tuberculosis* are significant problems in which host defense is affected by nutritional status. When recent immigrant populations are included, otherwise highly unusual parasitic infections must be considered as significant chronic infections in children living in developed countries.[213,214] In these infections, nutrient deficiencies are associated with reduced host defense. In contrast to studies in the mouse where short-term starvation induced hepatitis B viral replication,[215] dietary restriction of total calories, fat, iron, and protein in adult patients with chronic hepatitis C virus reduces serum alanine aminotransferase levels without adverse effect.[216]

HIV Infection

Malnutrition continues to be a significant problem in pediatric HIV infection. Studies show that micronutrient impairment is causally associated with the course of infection and progression of immune dysfunction.[217,218] Nutritional intervention may restore intestinal absorption and increase CD4 cell numbers.[219] Vitamin A deficiency is common in HIV infection and low maternal serum retinol level is a risk factor for mother-to-child transmission. Postpartum maternal and neonatal vitamin A supplementation of HIV-positive infants prolongs survival.[220] However, the same supplementation regimen increased progression to death for breast-fed children who were HIV negative at 6 weeks and infected through breast milk.[220] New studies have revealed a relationship between mannose-binding lectin (MBL) gene polymorphisms and response to vitamin A in HIV infection. MBL-2 allele variants are associated with deficiencies in innate immunity, which correlate with susceptibility to HIV infection. MBL is a component of the innate immune system that binds to carbohydrate ligands on the surface of many pathogens and activates the lectin pathway of the complement system. Study of HIV transmission in a supplementation study of vitamin A plus beta-carotene showed that infants with MBL-2 variants in the control arm showed increased maternal HIV transmission compared to the supplementation arm.[221] The study suggests that vitamin A plus beta-carotene corrected the effect of the MBL variant in increasing risk of HIV transmission. Selenium deficiency increases the virulence of HIV and enhances disease progression, whereas supplementation reduces high levels of IL-8 and TNF-alpha.[222] Lipodystrophy is an increasingly common complication of antiretroviral therapy for HIV infection that is prevalent in children. The lipodystrophy syndrome includes both fat accumulation and wasting, and is often accompanied by metabolic derangements in glucose and lipid metabolism.[223] Lipodystrophy appears to reflect a chronic mitochondrial toxicity that may be linked to HIV infection and L-carnitine deficiency.[224] L. carnitine is a nonessential micronutrient that regulates fatty acid transport into mitochondria and also modulates immune function and the effects of supplementation are currently being studied.

Tuberculosis

Generally declining rates of TB in industrialized countries have lead to less rigorous surveillance. However, TB is an important opportunistic pathogen that can lead to significant infection in persons with nutritional insufficiency such as anorexia nervosa[225] and is a major coinfection in HIV disease.[226] International adoptees are at high risk for TB and progression to active TB infection.[227] The natural history and clinical manifestations are different in children and are associated with the age at infection and the host immune status. Primary malnutrition increases the incidence and exacerbates clinical manifestations of TB infection. Experimental studies in the mouse have shown that PCM reduces production of IFN-gamma, TNF-alpha, and NO after infection leading to a decreased granulomatous reaction, higher lung bacillary load, and a more fatal TB course than in well nourished control mice, and that this could be reversed by restoring a diet with normal protein content.[228,229] Iron status is recognized as a potential cofactor in TB infection and progression since excess iron could enhance growth. Host polymorphisms in genes that regulate iron handling candidate genes, haptoglobin and natural- resistance-associated-macrophage protein-1, may be important discriminators for the pathogenesis of TB.[230] Selenium status also affects the pathogenesis of mycobacterial disease in adults with both HIV and TB infection.[231]

Vitamin D deficiency and vitamin D receptor polymorphisms are associated with an increased risk for TB infection.[232] In vitro studies show that 1,25-dihydroxyvitamin, the most active form of the vitamin, enhances mycobacterial killing by increasing NO production. Aerosol-challenge with *M. bovis* in the NO synthase 2 [NOS2(−/−)] deficient mouse leads to increased mycobacterial colonization and lesion formation compared to the wild-type mouse. Infected NOS2(−/−) mice developed severe necrotizing pyogranulomatous inflammation.[233] Lung colonization and lesion area of vitamin D deficient mice was greater compared to vitamin D replete mice, regardless of NOS2 phenotype demonstrating a fundamental role for vitamin D but also suggesting that vitamin D also has NO-independent effects. A role for the NO defense pathway human response to TB has been proposed.[234]

Endemic Infection

Parasitic infections cause malnutrition and impair host immune response, and are affected by host nutrition and immunity. Intestinal hookworm causes significant anemia.[235] Blood loss is directly proportional to the intensity of infection. Even a modest infection of *Necator americanus* can result in blood loss that exceeds physiologic daily requirements. Light infections of *Ancylostoma duodenale* may cause severe anemia in an infant that is difficult to correct with iron supplementation alone. Heavy infections with *Ascaris* may result in malabsorption, mild anemia, and wasting. The worm metabolizes vitamin A and heavy infections have been associated with vitamin A deficiency. Micronutrient deficiencies are common in parasitic infections.[236] Zinc deficiency impairs immune response to intestinal nematode infections at both systemic and intestinal level.[237] Infection also alters host nutritional since diarrhea promotes zinc loss. Giardiasis increases the serological levels of copper, while zinc and iron levels are decreased due to malabsorption.[238] CD4+ Th2 cells are critical for host protection while Th1 response actually inhibits protective immunity to nematode infection. IL-4, a Th2 cytokine, is required for protection and can also limit severity of infection. Protein malnutrition may increase the survival of nematode parasites by decreasing gut-associated IL-4 (Th-2) and increasing IFN-gamma (Th-1), leading to reduced intestinal and systemic Th-2 effector responses.[239]

One study of US immigrants reported that the most common pathogens were *Trichuris trichiura, Giardia lamblia,* and *A. lumbricoides. G. lamblia* was more prevalent in the younger than 5-year-old age group, and helminths were more prevalent in the 6- to 10-year-old age group. No helminths were found in immigrants who had been in the US for more than 3 years.

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Infection caused by intestinal parasites irritates the GI tract, causes pain, anorexia, flatulence, tenderness, and affects the host nutrition directly as a result of inflammatory and noninflammatory diarrhea. Host response mechanisms include accelerated epithelial cell turnover.[240] Trace element deficiencies affect the host pathogen interaction. Examples include the exacerbating effect of selenium deficiency on *Trypanosoma cruzi,* which is responsible for Chagas disease.[241] Malnutrition can cause an imbalance in T cell subpopulations that may lead to a defective T cell maturation and a decreased specific anti-*Ascaris* IgE response and worsens infection with *A. lumbricoides.*[242] Malaria causes the most serious nutritional consequences of any major parasite. It infects the placenta and compromises blood flow to the fetus, causing low-birth-weight. It also causes PCM in pregnant and lactating women and young children. Anemia, recurrent fever with acute phase cytokine responses, vomiting, and anorexia all produce adverse nutritional consequences in an already fragile child or pregnant woman. Recent investigation suggests that micronutrients such as vitamin A, vitamin E, and zinc may improve the morbidity of malaria through immune modulation and alteration of oxidative stress.[243]

REFERENCES

1. Brock AJ. Greek Medicine. London and Toronto: J.M. Dent and Sons; 1927.
2. Garrison, FH. An Introduction to History of Medicine. Philadelphia, PA: W.B. Saunders and Sons; 1929. 413ff.
3. Metchnikoff E. Virchow Archiv 1899;96:177.
4. Moulin AM. Immunology old and new: The beginning and the end. In: Paulin MH, editor. Essays on the History of Immunology. Toronto: Wall and Thompson; 1989. p. 292–8.
5. Smythe PM, Schonland M, Brereton-Stiles GG, et al. Thymolymphatic deficiency and depression of cell-mediated immunity in protein-calorie malnutrition. Lancet 1971;2:939–43.
6. Prentice AM. The thymus: A barometer of malnutrition. Br J Nutr 1999;81:345–7.
7. McDade TW, Beck MA, Kuzawa CW, Adair LS. Prenatal undernutrition and postnatal growth are associated with adolescent thymic function. J Nutr 2001;131:1225–31.
8. Moore SE, Collinson AC, Tamba N'Gom P, et al. Early immunological development and mortality from infectious disease in later life. Proc Nutr Soc 2006;65:311–8.
9. Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. J Infect Dis 2000;182:S62–8.
10. Dardenne M. Zinc and immune function. Eur J Clin Nutr 2002;56:S20–3.
11. Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. J Nutr 2000;130:1399S–406S.
12. Fraker PJ, King LE. Reprogramming of the immune system during zinc deficiency. Annu Rev Nutr 2004;24:277–98.
13. Haynes BF, Markert ML, Sempowski GD, et al. The role of the thymus in immune reconstitution in aging, bone marrow transplantation, and HIV-1 infection. Annu Rev Immunol 2000;18:529–60.
14. Mocchegiani E, Santarelli L, Costarelli L, et al. Plasticity of neuroendocrine-thymus interactions during ontogeny and ageing: Role of zinc and arginine. Ageing Res Rev 2006;5:281–309.
15. Mocchegiani E, Muzzioli M, Giacconi R, et al. Metallothioneins/PARP-1/IL-6 interplay on natural killer cell activity in elderly: Parallelism with nonagenarians and old infected humans. Effect of zinc supply. Mech Ageing Dev 2003;124:459–68.
16. Saha AR, Hadden EM, Hadden JW. Zinc induces thymulin secretion from human thymic epithelial cells in vitro and augments splenocyte and thymocyte responses in vivo. Int J Immunopharmacol 1995;17:729–33.
17. Haase H, Mocchegiani E, Rink L. Correlation between zinc status and immune function in the elderly. Biogerontology 2006;7:421–8.
18. Hoebe K, Janssen E, Beutler B. The interface between innate and adaptive immunity. Nat Immunol 2004;5:971–4.
19. Walker WA. Role of nutrients and bacterial colonization in the development of intestinal host defense. J Pediatr Gastroenterol Nutr 2000;30:S2–7.
20. Marodi L. Innate cellular immune responses in newborns. Clin Immunol 2006;118:137–44.
21. LeBouder E, Rey-Nores JE, Raby AC, et al. Modulation of neonatal microbial recognition: TLR-mediated innate immune responses are specifically and differentially modulated by human milk. J Immunol 2006;176:3742–52.
22. Lee JY, Plakidas A, Lee WH, et al. Differential modulation of toll-like receptors by fatty acids: Preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res 2003;44:479–86.
23. Bunout D, Barrera G, Hirsch S, et al. Effects of a nutritional supplement on the immune response and cytokine production in free-living Chilean elderly. JPEN J Parenter Enteral Nutr 2004;28:348–54.
24. Bussiere FI, Tridon A, Zimowska W, et al. Increase in complement component C3 is an early response to experimental magnesium deficiency in rats. Life Sci 2003;73:499–507.
25. Ekanem EE, Umotong AB, Raykundalia C, Catty D. Serum C-reactive protein and C3 complement protein levels in severely malnourished Nigerian children with and without bacterial infections. Acta Paediatr 1997;86:1317–20.
26. Kamath AB, Wang L, Das H, et al. Antigens in tea-beverage prime human Vgamma 2Vdelta 2 T cells in vitro and in vivo for memory and nonmemory antibacterial cytokine responses. Proc Natl Acad Sci U S A 2003;100:6009–14.
27. Erickson KL, Medina EA, Hubbard NE. Micronutrients and innate immunity. J Infect Dis 2000;182:S5–10.
28. Moret Y, Schmid-Hempel P. Survival for immunity: The price of immune system activation for bumblebee workers. Science 2000;290:1166–8.
29. Kudsk KA. Immunonutrition in surgery and critical care. Annu Rev Nutr 2006;26:463–79.
30. Ziegler TR, Evans ME, Fernandez-Estivariz C, Jones DP. Trophic and cytoprotective nutrition for intestinal adaptation, mucosal repair, and barrier function. Annu Rev Nutr 2003;23:229–61.
31. De-Souza DA, Greene LJ. Intestinal permeability and systemic infections in critically ill patients: Effect of glutamine. Crit Care Med 2005;33:1125–35.
32. Yeh SL, Lai YN, Shang HF, et al. Effects of glutamine supplementation on innate immune response in rats with gut-derived sepsis. Br J Nutr 2004;91:423–9.
33. Poindexter BB, Ehrenkranz RA, Stoll BJ, et al. Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants. Pediatrics 2004;113:1209–15.
34. Kapoor R, Huang YS. Gamma linolenic acid: An antiinflammatory omega-6 fatty acid. Curr Pharm Biotechnol 2006;7:531–4.
35. van Erk MJ, Blom WA, van Ommen B, Hendriks HF. High-protein and high-carbohydrate breakfasts differentially change the transcriptome of human blood cells. Am J Clin Nutr 2006;84:1233–41.
36. Gonzalez C, Gonzalez H, Rodriguez L, et al. Differential gene expression in lymphocytes from malnourished children. Cell Biol Int 2006;30:610–4.
37. Cousins RJ, Blanchard RK, Moore JB, et al. Regulation of zinc metabolism and genomic outcomes. J Nutr 2003;133:1521S–6S.
38. Sanderson IR, Naik S. Dietary regulation of intestinal gene expression. Annu Rev Nutr 2000;20:311–38.
39. Collins JF, Franck CA, Kowdley KV, Ghishan FK. Identification of differentially expressed genes in response to dietary iron deprivation in rat duodenum. Am J Physiol Gastrointest Liver Physiol 2005;288:G964–71.
40. Gelder CM, Hart KW, Williams OM, et al. Vitamin D receptor gene polymorphisms and susceptibility to Mycobacterium malmoense pulmonary disease. J Infect Dis 2000;181:2099–102.
41. Suneetha PV, Sarin SK, Goyal A, et al. Association between vitamin D receptor, CCR5, TNF-alpha and TNF-beta gene polymorphisms and HBV infection and severity of liver disease. J Hepatol 2006;44:856–63.
42. Anstead GM, Chandrasekar B, Zhang Q, Melby PC. Multinutrient undernutrition dysregulates the resident macrophage proinflammatory cytokine network, nuclear factor-kappaB activation, and nitric oxide production. J Leukoc Biol 2003;74:982–91.
43. Norton EB, Archibald LK, Nwanyanwu OC, et al. Clinical predictors of bloodstream infections and mortality in hospitalized Malawian children [discussion 151–5]. Pediatr Infect Dis J 2004;23:145–51.
44. Rodriguez L, Gonzalez C, Flores L, et al. Assessment by flow cytometry of cytokine production in malnourished children. Clin Diagn Lab Immunol 2005;12:502–7.
45. Dulger H, Arik M, Sekeroglu MR, et al. Pro-inflammatory cytokines in Turkish children with protein-energy malnutrition. Mediators Inflamm 2002;11:363–5.
46. Manary MJ, Yarasheski KE, Berger R, et al. Whole-body leucine kinetics and the acute phase response during acute infection in marasmic Malawian children. Pediatr Res 2004;55:940–6.
47. Phillips RS, Enwonwu CO, Okolo S, Hassan A. Metabolic effects of acute measles in chronically malnourished Nigerian children. J Nutr Biochem 2004;15:281–8.
48. Abraham K, Muller C, Gruters A, et al. Minimal inflammation, acute phase response and avoidance of misclassification of vitamin A and iron status in infants-importance of a high-sensitivity C-reactive protein (CRP) assay. Int J Vitam Nutr Res 2003;73:423–30.
49. Schultz C, Temming P, Bucsky P, et al. Immature anti-inflammatory response in neonates. Clin Exp Immunol 2004;135:130–6.
50. Ustianowski A, Shaffer R, Collin S, et al. Prevalence and associations of vitamin D deficiency in foreign-born persons with tuberculosis in London. J Infect 2005;50:432–7.
51. Singh M, Mynak ML, Kumar L, et al. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch Dis Child 2005;90:624–8.
52. Walker AS, Mulenga V, Sinyinza F, et al. Determinants of survival without antiretroviral therapy after infancy in HIV-1-infected Zambian children in the CHAP trial. J Acquir Immune Defic Syndr 2006;42:637–45.
53. He SX, Wu B, Chang XM, et al. Effects of selenium on peripheral blood mononuclear cell membrane fluidity, interleukin-2 production and interleukin-2 receptor expression in patients with chronic hepatitis. World J Gastroenterol 2004;10:3531–3.
54. Cunningham-Rundles S, McNeeley DF, Moon A. Mechanisms of nutrient modulation of the immune response. J Allergy Clin Immunol 2005;115:1119–28.
55. Cunningham-Rundles S. Evaluation of nutrient interaction in immune function. In: Calder PC, Field CJ, Gilled HS, editors. Nutrition and Immune Function. Oxon, UK: CABI; 2002. p. 21–39.
56. Cunningham-Rundles, S. Issues in the study of human immune function. In: Hughes DA, Darlington LG, Bendich A, editors. Dietary Enhancement of Human Immune Function. SCR Wallingford, Oxon, UK: Humana Press; 2003. p. 17–34.
57. Albers R, Bol M, Bleumink R, et al. Effects of supplementation with vitamins A, C, and E, selenium, and zinc on immune function in a murine sensitization model. Nutrition 2003;19:940–6.
58. Albert MJ, Qadri F, Wahed MA, et al. Supplementation with zinc, but not vitamin A, improves seroconversion to vibriocidal antibody in children given an oral cholera vaccine. J Infect Dis 2003;187:909–13.
59. Cunningham-Rundles S, McNeely D, Ananworanich JM. Immune response in malnutrition. In: Stiehm ER, Ochs HD, Winkelstein JA, editors. Immunologic Disorders in Infants and Children, 5th edition. Philadelphia, PA: Elsevier Saunders; 2004. p. 761–78.
60. Moynahan EJ. Letter: Acrodermatitis enteropathica: A lethal inherited human zinc-deficiency disorder. Lancet 1974;2:399–400.
61. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int 2003;23:139–42.
62. Caballero B. Global patterns of child health: The role of nutrition. Ann Nutr Metab 2002;46:3–7.
63. Scott ME, Koski KG. Zinc deficiency impairs immune responses against parasitic nematode infections at intestinal and systemic sites. J Nutr 2000;130:1412S–20S.
64. Anstead GM, Chandrasekar B, Zhao W, et al. Malnutrition alters the innate immune response and increases early visceralization following Leishmania donovani infection. Infect Immun 2001;69:4709–18.
65. Brewster DR, Manary MJ, Menzies IS, et al. Comparison of milk and maize based diets in kwashiorkor. Arch Dis Child 1997;76:242–8.
66. Sakamoto M, Fujisawa Y, Nishioka K. Physiologic role of the complement system in host defense, disease, and malnutrition. Nutrition 1998;14:391–8.
67. Peters-Golden M, Canetti C, Mancuso P, Coffey MJ. Leukotrienes: Underappreciated mediators of innate immune responses. J Immunol 2005;174:589–94.
68. Wang TT, Nestel FP, Bourdeau V, et al. Cutting edge: 1,25-Dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004;173:2909–12.

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69. Mancuso P, Gottschalk A, Phare SM, et al. Leptin-deficient mice exhibit impaired host defense in gram-negative pneumonia. J Immunol 2002;168:4018–24.
70. Ekiz C, Agaoglu L, Karakas Z, et al. The effect of iron deficiency anemia on the function of the immune system. Hematol J 2005;5:579–83.
71. Piemonti L, Monti P, Sironi M, et al. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 2000;164:4443–51.
72. Coutant F, Agaugue S, Perrin-Cocon L, et al. Sensing environmental lipids by dendritic cell modulates its function. J Immunol 2004;172:54–60.
73. Dylewski ML, Mastro AM, Picciano MF. Maternal selenium nutrition and neonatal immune system development. Biol Neonate 2002;82:122–7.
74. Vasquez-Garibay E, Campollo-Rivas O, Romero-Velarde E, et al. Effect of renutrition on natural and cell-mediated immune response in infants with severe malnutrition. J Pediatr Gastroenterol Nutr 2002;34:296–301.
75. Kozakova H, Hanson LA, Stepankova R, et al. Vitamin A deficiency leads to severe functional disturbance of the intestinal epithelium enzymes associated with diarrhoea and increased bacterial translocation in gnotobiotic rats. Microbes Infect 2003;5:405–11.
76. Rosales FJ. Vitamin A supplementation of vitamin A deficient measles patients lowers the risk of measles-related pneumonia in Zambian children. J Nutr 2002;132:3700–3.
77. Long KZ, Santos JI, Estrada Garcia T, et al. Vitamin A supplementation reduces the monocyte chemoattractant protein-1 intestinal immune response of Mexican children. J Nutr 2006;136:2600–5.
78. Quadro L, Gamble MV, Vogel S, et al. Retinol and retinol-binding protein: Gut integrity and circulating immunoglobulins. J Infect Dis 2000;182:S97–102.
79. Iwata M, Hirakiyama A, Eshima Y, et al. Retinoic acid imprints gut-homing specificity on T cells. Immunity 2004;21:527–38.
80. Mora JR, Iwata M, Eksteen B, et al. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science 2006;314:1157–60.
81. Pesonen M, Kallio MJ, Siimes MA, Ranki A. Retinol concentrations after birth are inversely associated with atopic manifestations in children and young adults. Clin Exp Allergy 2007;37:54–61.
82. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. Am J Clin Nutr 2004;80:1717S–20S.
83. Simmons JD, Mullighan C, Welsh KI, Jewell DP. Vitamin D receptor gene polymorphism: Association with Crohn's disease susceptibility. Gut 2000;47:211–4.
84. Wayse V, Yousafzai A, Mogale K, Filteau S. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. Eur J Clin Nutr 2004;58:563–7.
85. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770–3.
86. Buck RH, Thomas DL, Winship TR, et al. Effect of dietary ribonucleotides on infant immune status. Part 2: Immune cell development. Pediatr Res 2004;56:891–900.
87. Schaller JP, Kuchan MJ, Thomas DL, et al. Effect of dietary ribonucleotides on infant immune status. Part 1: Humoral responses. Pediatr Res 2004;56:883–90.
88. Martinez-Augustin O, Boza JJ, Navarro J, et al. Dietary nucleotides may influence the humoral immunity in immunocompromised children. Nutrition 1997;13:465–9.
89. Hawkes JS, Gibson RA, Roberton D, Makrides M. Effect of dietary nucleotide supplementation on growth and immune function in term infants: A randomized controlled trial. Eur J Clin Nutr 2006;60:254–64.
90. Carver JD, Stromquist CI. Dietary nucleotides and preterm infant nutrition. J Perinatol 2006;26:443–4.
91. Walker WA. The dynamic effects of breastfeeding on intestinal development and host defense. Adv Exp Med Biol 2004;554:155–70.
92. Kelly D, Coutts AG. Early nutrition and the development of immune function in the neonate. Proc Nutr Soc 2000;59:177–85.
93. Newburg DS, Ruiz-Palacios GM, Morrow AL. Human milk glycans protect infants against enteric pathogens. Annu Rev Nutr 2005;25:37–58.
94. Jarvinen KM, Laine ST, Jarvenpaa AL, Suomalainen HK. Does low IgA in human milk predispose the infant to development of cow's milk allergy? Pediatr Res 2000;48:457–62.
95. Dvorak B, Fituch CC, Williams CS, et al. Increased epidermal growth factor levels in human milk of mothers with extremely premature infants. Pediatr Res 2003;54:15–9.
96. Collinson AC, Moore SE, Cole TJ, Prentice AM. Birth season and environmental influences on patterns of thymic growth in rural Gambian infants. Acta Paediatr 2003;92:1014–20.
97. Basu S, Sengupta B, Paladhi PK. Single megadose vitamin A supplementation of Indian mothers and morbidity in breastfed young infants. Postgrad Med J 2003;79:397–402.
98. Vidal K, Labeta MO, Schiffrin EJ, Donnet-Hughes A. Soluble CD14 in human breast milk and its role in innate immune responses. Acta Odontol Scand 2001;59:330–4.
99. Dunstan JA, Roper J, Mitoulas L, et al. The effect of supplementation with fish oil during pregnancy on breast milk immunoglobulin A, soluble CD14, cytokine levels and fatty acid composition. Clin Exp Allergy 2004;34:1237–42.
100. Accorsi S, Fabiani M, Nattabi B, et al. The disease profile of poverty: Morbidity and mortality in northern Uganda in the context of war, population displacement and HIV/AIDS. Trans R Soc Trop Med Hyg 2005;99:226–33.
101. Carvalho NF, Kenney RD, Carrington PH, Hall DE. Severe nutritional deficiencies in toddlers resulting from health food milk alternatives. Pediatrics 2001;107:E46.
102. Eastlack JP, Grande KK, Levy ML, Nigro JF. Dermatosis in a child with kwashiorkor secondary to food aversion. Pediatr Dermatol 1999;16:95–102.
103. Liu T, Howard RM, Mancini AJ, et al. Kwashiorkor in the United States: Fad diets, perceived and true milk allergy, and nutritional ignorance. Arch Dermatol 2001;137:630–6.
104. Ganji V, Hampl JS, Betts NM. Race-, gender- and age-specific differences in dietary micronutrient intakes of US children. Int J Food Sci Nutr 2003;54:485–90.
105. Fattal-Valevski A, Kesler A, Sela BA, et al. Outbreak of life-threatening thiamine deficiency in infants in Israel caused by a defective soy-based formula. Pediatrics 2005;115:e233–8.
106. Obladen M, Loui A, Kampmann W, Renz H. Zinc deficiency in rapidly growing preterm infants. Acta Paediatr 1998;87:685–91.
107. Kaur S, Thami GP, Kanwar AJ. Acrodermatitis enteropathica in a full-term breast-fed infant. Indian J Pediatr 2002;69:631–3.
108. Kury S, Kharfi M, Kamoun R, et al. Mutation spectrum of human SLC39A4 in a panel of patients with acrodermatitis enteropathica. Hum Mutat 2003;22:337–8.
109. Madhok AB, Chandrasekran A, Parnell V, et al. Levels of recent thymic emigrant cells decrease in children undergoing partial thymectomy during cardiac surgery. Clin Diagn Lab Immunol 2005;12:563–5.
110. Jawad AF, McDonald-Mcginn DM, Zackai E, Sullivan KE. Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pediatr 2001;139:715–23.
111. Van Esch H, Groenen P, Nesbit MA, et al. GATA3 haplo-insufficiency causes human HDR syndrome. Nature 2000;406:419–22.
112. Aaby P, Marx C, Trautner S, et al. Thymus size at birth is associated with infant mortality: A community study from Guinea-Bissau. Acta Paediatr 2002;91:698–703.
113. Faggioni R, Feingold KR, Grunfeld C. Leptin regulation of the immune response and the immunodeficiency of malnutrition. FASEB J 2001;15:2565–71.
114. Savino W. The thymus gland is a target in malnutrition. Eur J Clin Nutr 2002;56:S46–9.
115. Palacio A, Lopez M, Perez-Bravo F, et al. Leptin levels are associated with immune response in malnourished infants. J Clin Endocrinol Metab 2002;87:3040–6.
116. Reid M, Badaloo A, Forrester T, et al. The acute-phase protein response to infection in edematous and nonedematous protein-energy malnutrition. Am J Clin Nutr 2002;76:1409–15.
117. Russell BJ, White AV, Newbury J, et al. Evaluation of hospitalisation for Indigenous children with malnutrition living in Central Australia. Aust J Rural Health 2004;12:187–91.
118. Najera O, Gonzalez C, Toledo G, et al. Flow cytometry study of lymphocyte subsets in malnourished and well-nourished children with bacterial infections. Clin Diagn Lab Immunol 2004;11:577–80.
119. Rikimaru T, Taniguchi K, Yartey JE, et al. Humoral and cell-mediated immunity in malnourished children in Ghana. Eur J Clin Nutr 1998;52:344–50.
120. Forte WC, Santos de Menezes MC, Horta C, Carneiro Leao Bach R. Serum IgE level in malnutrition. Allergol Immunopathol (Madr) 2003;31:83–6.
121. Moore SE, Goldblatt D, Bates CJ, Prentice AM. Impact of nutritional status on antibody responses to different vaccines in undernourished Gambian children. Acta Paediatr 2003;92:170–6.
122. Barker DJ. The developmental origins of chronic adult disease. Acta Paediatr Suppl 2004;93:26–33.
123. Dobbing J. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341:1421–2.
124. McDade TW, Beck MA, Kuzawa C, Adair LS. Prenatal undernutrition, postnatal environments, and antibody response to vaccination in adolescence. Am J Clin Nutr 2001;74:543–8.
125. Dagogo-Jack S, Tykodi G, Umamaheswaran I. Inhibition of cortisol biosynthesis decreases circulating leptin levels in obese humans. J Clin Endocrinol Metab 2005;90:5333–5.
126. Bornstein SR, Licinio J, Tauchnitz R, et al. Plasma leptin levels are increased in survivors of acute sepsis: Associated loss of diurnal rhythm, in cortisol and leptin secretion. J Clin Endocrinol Metab 1998;83:280–3.
127. Gibson WT, Farooqi IS, Moreau M, et al. Congenital leptin deficiency due to homozygosity for the Delta133G mutation: Report of another case and evaluation of response to four years of leptin therapy. J Clin Endocrinol Metab 2004;89:4821–6.
128. Otero M, Lago R, Gomez R, et al. Towards a pro-inflammatory and immunomodulatory emerging role of leptin. Rheumatology 2006;45:944–50.
129. Levin BE. Factors promoting and ameliorating the development of obesity. Physiol Behav 2005;86:633–9.
130. Vieira VJ, Ronan AM, Windt MR, Tagliaferro AR. Elevated atopy in healthy obese women. Am J Clin Nutr 2005;82:504–9.
131. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006;6:438–46.
132. Tanaka S, Inoue S, Isoda F, et al. Impaired immunity in obesity: Suppressed but reversible lymphocyte responsiveness. Int J Obes Relat Metab Disord 1993;17:631–6.
133. Skibola CF, Holly EA, Forrest MS, et al. Body mass index, leptin and leptin receptor polymorphisms, and non-hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2004;13:779–86.
134. Wernstedt I, Eriksson AL, Berndtsson A, et al. A common polymorphism in the interleukin-6 gene promoter is associated with overweight. Int J Obes Relat Metab Disord 2004;28:1272–9.
135. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A 2004;101:15718–23.
136. Dhurandhar NV. Contribution of pathogens in human obesity. Drug News Perspect 2004;17:307–13.
137. Juyal R, Osmamy M, Black RE, et al. Efficacy of micronutrient fortification of milk on morbidity in pre-school children and growth-a double blind randomised controlled trial. Asia Pac J Clin Nutr 2004;13:S44.
138. Lyons GH, Stangoulis JC, Graham RD. Exploiting micronutrient interaction to optimize biofortification programs: The case for inclusion of selenium and iodine in the HarvestPlus program. Nutr Rev 2004;62:247–52.
139. Beck MA, Williams-Toone D, Levander OA. Coxsackievirus B3-resistant mice become susceptible in Se/vitamin E deficiency. Free Radic Biol Med 2003;34:1263–70.
140. van den Broek N. Anaemia and micronutrient deficiencies. Br Med Bull 2003;67:149–60.
141. Klinger G, Shamir R, Singer P, et al. Parenteral selenium supplementation in extremely low birth weight infants: Inadequate dosage but no correlation with hypothyroidism. J Perinatol 1999;19:568–72.
142. Nair S, Norkus EP, Hertan H, Pitchumoni CS. Micronutrient antioxidants in gastric mucosa and serum in patients with gastritis and gastric ulcer: Does *Helicobacter pylori* infection affect the mucosal levels? J Clin Gastroenterol 2000;30:381–5.
143. Baysoy G, Ertem D, Ademoglu E, et al. Gastric histopathology, iron status and iron deficiency anemia in children with *Helicobacter pylori* infection. J Pediatr Gastroenterol Nutr 2004;38:146–51.
144. Bennedsen M, Wang X, Willen R, et al. Treatment of *H. pylori* infected mice with antioxidant astaxanthin reduces gastric inflammation, bacterial load and modulates cytokine release by splenocytes. Immunol Lett 1999;70:185–9.
145. Olczak AA, Seyler RW, Jr, Olson JW, Maier RJ. Association of *Helicobacter pylori* antioxidant activities with host colonization proficiency. Infect Immun 2003;71:580–3.
146. Goth SR, Chu RA, Gregg JP, et al. Uncoupling of ATP-mediated calcium signaling and dysregulated interleukin-6 secretion in dendritic cells by nanomolar thimerosal. Environ Health Perspect 2006;114:1083–91.
147. Brewster UC, Perazella MA. Intravenous iron and the risk of infection in end-stage renal disease patients. Semin Dial 2004;17:57–60.
148. Chung BH, Ha SY, Chan GC, et al. *Klebsiella* infection in patients with thalassemia. Clin Infect Dis 2003;36:575–9.
149. Cunningham-Rundles S, Giardina PJ, Grady RW, et al. Effect of transfusional iron overload on immune response. J Infect Dis 2000;182:S115–21.

150. Nasr MR, Ali S, Shaker M, Elgabry E. Antioxidant micronutrients in children with thalassaemia in Egypt. East Mediterr Health J 2002;8:490–5.
151. Moalem S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: Implications for infectious disease and survival. Biometals 2004;17:135–9.
152. Fritsche G, Larcher C, Schennach H, Weiss G. Regulatory interactions between iron and nitric oxide metabolism for immune defense against *Plasmodium falciparum* infection. J Infect Dis 2001;183:1388–94.
153. Berger J, Dyck JL, Galan P, et al. Effect of daily iron supplementation on iron status, cell-mediated immunity, and incidence of infections in 6–36 month old Togolese children. Eur J Clin Nutr 2000;54:29–35.
154. Sanders TA. Vegetarian diets and children. Pediatr Clin North Am 1995;42:955–65.
155. Mattsson N, Kilander A, Bjornsson E. *Helicobacter pylori* can in rare cases be the cause of iron and vitamin B12 deficiency. No increased risk of iron and vitamin B12 deficiency due to proton pump inhibitors. Lakartidningen 2004;101:2014–5.
156. Lopez A. Malnutrition and the burden of disease. Asia Pac J Clin Nutr 2004;13:S7.
157. Bhatnagar S, Natchu UC. Zinc in child health and disease. Indian J Pediatr 2004;71:991–5.
158. Bhaskaram P. Micronutrient malnutrition, infection, and immunity: An overview. Nutr Rev 2002;60:S40–5.
159. Crone J, Huber WD, Eichler I, Granditsch G. Acrodermatitis enteropathica-like eruption as the presenting sign of cystic fibrosis—case report and review of the literature. Eur J Pediatr 2002;161:475–8.
160. Mocchegiani E, Ciavattini A, Santarelli L, et al. Role of zinc and alpha2 macroglobulin on thymic endocrine activity and on peripheral immune efficiency (natural killer activity and interleukin 2) in cervical carcinoma. Br J Cancer 1999;79:244–50.
161. Fraker PJ. Roles for cell death in zinc deficiency. J Nutr 2005;135:359–62.
162. Fraker PJ, Lill-Elghanian DA. The many roles of apoptosis in immunity as modified by aging and nutritional status. J Nutr Health Aging 2004;8:56–63.
163. Raqib R, Roy SK, Rahman MJ, et al. Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. Am J Clin Nutr 2004;79:444–50.
164. von Bulow V, Rink L, Haase H. Zinc-mediated inhibition of cyclic nucleotide phosphodiesterase activity and expression suppresses TNF-alpha and IL-1 beta production in monocytes by elevation of guanosine 3',5'-cyclic monophosphate. J Immunol 2005;175:4697–705.
165. Metz CH, Schroder AK, Overbeck S, et al. T-helper type 1 cytokine release is enhanced by in vitro zinc supplementation due to increased natural killer cells. Nutrition 2006.
166. Qadri F, Ahmed T, Wahed MA, et al. Suppressive effect of zinc on antibody response to cholera toxin in children given the killed, B subunit-whole cell, oral cholera vaccine. Vaccine 2004;22:416–21.
167. Kury S, Dreno B, Bezieau S, et al. Identification of *SLC39A4*, a gene involved in acrodermatitis enteropathica. Nat Genet 2002;31:239–40.
168. Cousins RJ, Blanchard RK, Popp MP, et al. A global view of the selectivity of zinc deprivation and excess on genes expressed in human THP-1 mononuclear cells. Proc Natl Acad Sci U S A 2003;100:6952–7.
169. Aydemir TB, Blanchard RK, Cousins RJ. Zinc supplementation of young men alters metallothionein, zinc transporter, and cytokine gene expression in leukocyte populations. Proc Natl Acad Sci U S A 2006;103:1699–704.
170. Schlesinger L, Arevalo M, Arredondo S, et al. Effect of a zinc-fortified formula on immunocompetence and growth of malnourished infants. Am J Clin Nutr 1992;56:491–8.
171. Thakur S, Gupta N, Kakkar P. Serum copper and zinc concentrations and their relation to superoxide dismutase in severe malnutrition. Eur J Pediatr 2004.
172. Marikovsky M, Ziv V, Nevo N, et al. Cu/Zn superoxide dismutase plays important role in immune response. J Immunol 2003;170:2993–3001.
173. Botash AS, Nasca J, Dubowy R, et al. Zinc-induced copper deficiency in an infant. Am J Dis Child 1992;146:709–11.
174. Percival SS. Copper and immunity. Am J Clin Nutr 1998;67:1064S–8S.
175. Bonham M, O'Connor JM, Hannigan BM, Strain JJ. The immune system as a physiological indicator of marginal copper status? Br J Nutr 2002;87:393–403.
176. Squali Houssaini FZ, Iraqi MR, Arnaud J, et al. Trace elements and protein-calorie malnutrition in the Fes area (Morocco). Biomed Pharmacother 1997;51:349–51.
177. Miyajima H, Takahashi Y, Kono S. Aceruloplasminemia, an inherited disorder of iron metabolism. Biometals 2003;16:205–13.
178. Cox DW, Moore SD. Copper transporting P-type ATPases and human disease. J Bioenerg Biomembr 2002;34:333–8.
179. Rayman MP. The importance of selenium to human health. Lancet 2000;356:233–41.
180. Thomson CD. Selenium and iodine intakes and status in New Zealand and Australia. Br J Nutr 2004;91:661–72.
181. Manar MJ, MacPherson GD, McArdle F, et al. Selenium status, kwashiorkor and congestive heart failure. Acta Paediatr 2001;90:950–2.
182. Beck MA, Levander OA, Handy J. Selenium deficiency and viral infection. J Nutr 2003;133:1463S–7S.
183. Salonen JT, Alfthan G, Huttunen JK, Puska P. Association between serum selenium and the risk of cancer. Am J Epidemiol 1984;120:342–9.
184. Virtamo J, Valkeila E, Alfthan G, et al. Serum selenium and risk of cancer. A prospective follow-up of nine years. Cancer 1987;60:145–8.
185. Ferencik M, Ebringer L. Modulatory effects of selenium and zinc on the immune system. Folia Microbiol (Praha) 2003;48:417–26.
186. Baum MK, Shor-Posner G, Lai S, et al. High risk of HIV-related mortality is associated with selenium deficiency. J Acquir Immune Defic Syndr Hum Retrovirol 1997;15:370–4.
187. Baeten JM, Mostad SB, Hughes MP, et al. Selenium deficiency is associated with shedding of HIV-1-infected cells in the female genital tract. J Acquir Immune Defic Syndr 2001;26:360–4.
188. Stephensen CB. Vitamin A, infection, and immune function. Annu Rev Nutr 2001;21:167–92.
189. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. A meta-analysis. JAMA 1993;269:898–903.
190. Sommer A, Davidson FR. Assessment and control of vitamin A deficiency: The Annecy Accords. J Nutr 2002;132:2845S–2850S.
191. Cunningham-Rundles S, Kim SH, Dnistrian A, et al. Micronutrient and cytokine interaction in congenital pediatric HIV infection. J Nutr 1996;126:2674S–2679S.
192. Al-Kubaisy W, Al-Rubaiy MG, Nassief HA. Xerophthalmia among hospitalized Iraqi children. East Mediterr Health J 2002;8:496–502.
193. Tan Z, Ma G, Lin L, et al. Prevalence of subclinical vitamin A deficiency and its affecting factors in 8669 children of China. Zhonghua Yu Fang Yi Xue Za Zhi 2002;36:161–3.
194. Cser MA, Majchrzak D, Rust P, et al. Serum carotenoid and retinol levels during childhood infections. Ann Nutr Metab 2004;48:156–62.
195. Aukrust P, Muller F, Ueland T, et al. Decreased vitamin A levels in common variable immunodeficiency: Vitamin A supplementation in vivo enhances immunoglobulin production and downregulates inflammatory responses. Eur J Clin Invest 2000;30:252–9.
196. Wieringa FT, Dijkhuizen MA, West CE, et al. Reduced production of immunoregulatory cytokines in vitamin A- and zinc-deficient Indonesian infants. Eur J Clin Nutr 2004;58:1498–504.
197. Stephensen CB, Jiang X, Freytag T. Vitamin A deficiency increases the in vivo development of IL-10-positive Th2 cells and decreases development of Th1 cells in mice. J Nutr 2004;134:2660–6.
198. Grubesic RB, Selwyn BJ. Vitamin A supplementation and health outcomes for children in Nepal. J Nurs Scholarsh 2003;35:15–20.
199. Long KZ, Estrada-Garcia T, Rosado JL, et al. The effect of vitamin A supplementation on the intestinal immune response in Mexican children is modified by pathogen infections and diarrhea. J Nutr 2006;136:1365–70.
200. Park OJ, Kim HY, Kim WK, et al. Effect of vitamin E supplementation on antioxidant defense systems and humoral immune responses in young, middle-aged and elderly Korean women. J Nutr Sci Vitaminol (Tokyo) 2003;49:94–9.
201. van Tits LJ, Demacker PN, de Graaf J, et al. Alpha-tocopherol supplementation decreases production of superoxide and cytokines by leukocytes ex vivo in both normolipidemic and hypertriglyceridemic individuals. Am J Clin Nutr 2000;71:458–64.
202. Wu D, Meydani SN. Mechanism of age-associated up-regulation in macrophage PGE2 synthesis. Brain Behav Immun 2004;18:487–94.
203. Lee CY, Man-Fan Wan J. Vitamin E supplementation improves cell-mediated immunity and oxidative stress of Asian men and women. J Nutr 2000;130:2932–7.
204. Malmberg KJ, Lenkei R, Petersson M, et al. A short-term dietary supplementation of high doses of vitamin E increases T helper 1 cytokine production in patients with advanced colorectal cancer. Clin Cancer Res 2002;8:1772–8.
205. Pighetti GM, Eskew ML, Reddy CC, Sordillo LM. Selenium and vitamin E deficiency impair transferrin receptor internalization but not IL-2, IL-2 receptor, or transferrin receptor expression. J Leukoc Biol 1998;63:131–7.
206. Lagrange-Puget M, Durieu I, Ecochard R, et al. Longitudinal study of oxidative status in 312 cystic fibrosis patients in stable state and during bronchial exacerbation. Pediatr Pulmonol 2004;38:43–9.
207. Hartel C, Strunk T, Bucsky P, Schultz C. Effects of vitamin C on intracytoplasmic cytokine production in human whole blood monocytes and lymphocytes. Cytokine 2004;27:101–6.
208. Victor VV, Guayerbas N, Puerto M, et al. Ascorbic acid modulates in vitro the function of macrophages from mice with endotoxic shock. Immunopharmacology 2000;46:89–101.
209. Fischer CP, Hiscock NJ, Penkowa M, et al. Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. J Physiol 2004;558:633–45.
210. Ahmed J, Zaman MM, Ali SM. Immunological response to antioxidant vitamin supplementation in rural Bangladeshi school children with group A streptococcal infection. Asia Pac J Clin Nutr 2004;13:226–30.
211. Wintergerst ES, Maggini S, Hornig DH. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann Nutr Metab 2006;50:85–94.
212. Akyon Y. Effect of antioxidants on the immune response of *Helicobacter pylori*. Clin Microbiol Infect 2002;8:438–41.
213. Schwarzwald H. Illnesses among recently immigrated children. Semin Pediatr Infect Dis 2005;16:78–83.
214. Salas SD, Heifetz R, Barrett-Connor E. Intestinal parasites in Central American immigrants in the United States. Arch Intern Med 1990;150:1514–6.
215. Shlomai A, Paran N, Shaul Y. PGC-1alpha controls hepatitis B virus through nutritional signals. Proc Natl Acad Sci U S A 2006;103:16003–8.
216. Iwasa M, Iwata K, Kaito M, et al. Efficacy of long-term dietary restriction of total calories, fat, iron, and protein in patients with chronic hepatitis C virus. Nutrition 2004;20:368–71.
217. van Lettow M, West CE, van der Meer JW, et al. Low plasma selenium concentrations, high plasma human immunodeficiency virus load and high interleukin-6 concentrations are risk factors associated with anemia in adults presenting with pulmonary tuberculosis in Zomba district, Malawi. Eur J Clin Nutr 2005;59:526–32.
218. Guarino A, Bruzzese E, De Marco G, Buccigrossi V. Management of gastrointestinal disorders in children with HIV infection. Paediatr Drugs 2004;6:347–62.
219. Guarino A, Spagnuolo MI, Giacomet V, et al. Effects of nutritional rehabilitation on intestinal function and on CD4 cell number in children with HIV. J Pediatr Gastroenterol Nutr 2002;34:366–71.
220. Humphrey JH, Iliff PJ, Marinda ET, et al. Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. J Infect Dis 2006;193:860–71.
221. Kuhn L, Coutsoudis A, Trabattoni D, et al. Synergy between mannose-binding lectin gene polymorphisms and supplementation with vitamin A influences susceptibility to HIV infection in infants born to HIV-positive mothers. Am J Clin Nutr 2006;84:610–5.
222. Baum MK, Miguez-Burbano MJ, Campa A, Shor-Posner G. Selenium and interleukins in persons infected with human immunodeficiency virus type 1. J Infect Dis 2000;182:S69–73.
223. Ergun-Longmire B, Lin-Su K, Dunn AM, et al. Effects of protease inhibitors on glucose tolerance, lipid metabolism, and body composition in children and adolescents infected with human immunodeficiency virus. Endocr Pract 2006;12:514–21.
224. Day L, Shikuma C, Gerschenson M. Acetyl-L-carnitine for the treatment of HIV lipoatrophy. Ann N Y Acad Sci 2004;1033:139–46.
225. Hotta M, Nagashima E, Takagi S, et al. Two young female patients with anorexia nervosa complicated by Mycobacterium tuberculosis infection. Intern Med 2004;43:440–4.
226. Hesseling AC, Westra AE, Werschkull H, et al. Outcome of HIV infected children with culture confirmed tuberculosis. Arch Dis Child 2005;90:1171–4.
227. Miller LC. International adoption: Infectious diseases issues. Clin Infect Dis 2005;40:286–93.
228. Boelaert JR, Gordeuk VR. Protein energy malnutrition and risk of tuberculosis infection. Lancet 2002;360:1102.
229. Chan J, Tian Y, Tanaka KE, et al. Effects of protein calorie malnutrition on tuberculosis in mice. Proc Natl Acad Sci U S A 1996;93:14857–61.

230. McDermid JM, Prentice AM. Iron and infection: Effects of host iron status and the iron-regulatory genes haptoglobin and NRAMP1 (SLC11A1) on host-pathogen interactions in tuberculosis and HIV. Clin Sci (Lond) 2006;110:503–24.
231. Shor-Posner G, Miguez MJ, Pineda LM, et al. Impact of selenium status on the pathogenesis of mycobacterial disease in HIV-1-infected drug users during the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2002;29:169–73.
232. Wilkinson RJ, Llewelyn M, Toossi Z, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: A case-control study. Lancet 2000;355:618–21.
233. Waters WR, Palmer MV, Nonnecke BJ, et al. Mycobacterium bovis infection of vitamin D-deficient NOS2–/–mice. Microb Pathog 2004;36:11–7.
234. Nathan C. Role of iNOS in human host defense. Science 2006;312:1874–5; author reply 1874–5.
235. Stoltzfus RJ, Chway HM, Montresor A, et al. Low dose daily iron supplementation improves iron status and appetite but not anemia, whereas quarterly anthelminthic treatment improves growth, appetite and anemia in Zanzibari preschool children. J Nutr 2004;134:348–56.
236. Hesham MS, Edariah AB, Norhayati M. Intestinal parasitic infections and micronutrient deficiency: A review. Med J Malaysia 2004;59:284–93.
237. Koski KG, Scott ME. Gastrointestinal nematodes, nutrition and immunity: Breaking the negative spiral. Annu Rev Nutr 2001;21:297–321.
238. Ertan P, Yereli K, Kurt O, et al. Serological levels of zinc, copper and iron elements among Giardia lamblia infected children in Turkey. Pediatr Int 2002;44:286–8.
239. Ing R, Su Z, Scott ME, Koski KG. Suppressed T helper 2 immunity and prolonged survival of a nematode parasite in protein-malnourished mice. Proc Natl Acad Sci U S A 2000;97:7078–83.
240. Cliffe LJ, Humphreys NE, Lane TE, et al. Accelerated intestinal epithelial cell turnover: A new mechanism of parasite expulsion. Science 2005;308:1463–5.
241. Rivera MT, De Souza AP, Araujo-Jorge TC, et al. Trace elements, innate immune response and parasites. Clin Chem Lab Med 2003;41:1020–5.
242. Hagel I, Lynch NR, Puccio F, et al. Defective regulation of the protective IgE response against intestinal helminth Ascaris lumbricoides in malnourished children. J Trop Pediatr 2003;49:136–42.
243. Nussenblatt V, Semba RD. Micronutrient malnutrition and the pathogenesis of malarial anemia. Acta Trop 2002;82:321–37.

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