

Molecular mechanisms in allergy and clinical immunology

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Mechanisms of nutrient modulation of the immune response

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Lack of adequate macronutrients or selected micronutrients, especially zinc, selenium, iron, and the antioxidant vitamins, can lead to clinically significant immune deficiency and infections in children. Undernutrition in critical periods of gestation and neonatal maturation and during weaning impairs the development and differentiation of a normal immune system. Infections are both more frequent and more often become chronic in the malnourished child. Recent identification of genetic mechanisms is revealing critical pathways in the gastrointestinal immune response. New studies show that the development of tolerance, control of inflammation, and response to normal mucosal flora are interrelated and linked to specific immune mechanisms. Nutrients act as antioxidants and as cofactors at the level of cytokine regulation. Protein calorie malnutrition and zinc deficiency activate the hypothalamic-pituitary-adrenal axis. Increased circulating levels of glucocorticoids cause thymic atrophy and affect hematopoiesis. Chronic undernutrition and micronutrient deficiency compromise cytokine response and affect immune cell trafficking. The combination of chronic undernutrition and infection further weakens the immune response, leading to altered immune cell populations and a generalized increase in inflammatory mediators. Obesity caused by excess nutrition or excess storage of fats relative to energy expenditure is a form of malnutrition that is increasingly seen in children. Leptin is emerging as a cytokine-like immune regulator that has complex effects in both overnutrition and in the inflammatory response in malnutrition. Because the immune system is immature at birth, malnutrition in childhood might have long-term effects on health. (*J Allergy Clin Immunol* 2005;115:1119-28.)

Key words: Mucosal immune response, nutrition, protein calorie malnutrition, micronutrient, infection, cytokine, antioxidant vitamins, trace elements, zinc, HIV, parasitic infection, children

Primary malnutrition caused by an inadequate supply of either macronutrients or selected micronutrients can lead to clinically significant immune deficiency and infections in children.¹⁻⁴ The development of a normal immune system will be impaired by undernutrition in critical periods of gestation and neonatal maturation and during weaning.^{4,5} Infections are both more frequent and more often become chronic in the malnourished child. The interaction of chronic undernutrition and infection further weakens the immune response, leading to altered immune cell populations^{6,7} and a generalized increase in inflammatory mediators.⁸ Reduction of leukotrienes, which enhance leukocyte accumulation and phagocyte capacity, impairs microbial ingestion and killing.⁹ The overall effects might include altered microbial colonization of mucosal surfaces and impaired host response to new pathogens.^{10,11} Selective micronutrient deficiencies alone also cause specific immune deficiencies and have long-term consequences for host defense in the developing child.¹²⁻¹⁴ The cellular immune system is more directly affected in protein calorie malnutrition (PCM) than the humoral immune system.¹⁵⁻¹⁷ The structure and function of the thymus is damaged, and T-cell memory response to antigens is reduced.^{6,7} In contrast, short-term seroconversion to whole inactivated viral and bacterial polysaccharide vaccines can be achieved in malnourished children, and antibody titers to common pathogens might be normal.^{18,19} Micronutrient deficiencies will affect the adaptive antibody and cellular immune response, as well as the innate immune response.^{14,20-22}

Overweight status and obesity are increasingly common among children.²³ Current studies suggest that leptin, which is both a hormone regulating satiety and a cytokine-like immune regulator, and ghrelin, the natural ligand for the growth hormone secretagogue receptor in the pituitary gland, link fat regulation and the immune system.^{24,25} The cause of eating disorders might involve these mechanisms, explaining why a deficient immune response is observed in patients with bulimia and anorexia nervosa.²⁶

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Abbreviations used

- AE: Acrodermatitis enteropathica
HPA axis: Hypothalamic-pituitary-adrenal axis
NK: Natural killer
PCM: Protein calorie malnutrition

In this review we will discuss new advances in the study of nutrient modulation of the immune response that illuminate how critical mechanisms of host defense might be affected in the malnourished child.

PRIMARY MALNUTRITION

PCM is a major common cause of secondary immune deficiency in the world. Deficiencies are usually complex, frequently involving both protein calorie and varying degrees of micronutrient deficiency of vitamin A, vitamin E, vitamin B₆, folate, zinc, iron, copper, and selenium.^{2,27,28} On the basis of severity and features at presentation, PCM is defined as marasmus, a chronic wasting condition, or kwashiorkor, which is distinguished by edema and anemia. Marasmus occurs when there is insufficiency of all foods, whereas kwashiorkor develops from deficiency of protein in a diet that might be high in calories.

Kwashiorkor, a West African word that means “the disease that occurs when the next baby is born” is more common after weaning and is characterized by moderate growth retardation, dermatitis, edema, moon facies, and hepatosplenomegaly. Very low albumin levels and anemia are usually found. One example of the appearance of the child with kwashiorkor is shown in Fig 1. Kwashiorkor might develop in previously healthy children who are inadvertently placed on a low-protein diet because of presumed food intolerance.²⁹

Marasmus is often associated with early weaning. This condition is characterized by chronic wasting and gross underweight status. Edema and hair changes are absent. The skin is wrinkled, and the facial bones become prominent. The infants are severely anemic, with low transferrin levels, reduced albumin levels, and zinc deficiency. Loss of selenium is greater in infants with marasmus compared with that seen in those with kwashiorkor.³⁰ The presentation of PCM, including the age of the child, is critical for severity of immune deficiency and mortality.³¹ Many more children in developing countries have slow growth, low-grade infections, and low energy levels, without overt manifestations of malnutrition.³²

Primary malnutrition leads to atrophy of the lymphoid organs, profound T-lymphocyte deficiency, and increased susceptibility to pathogens, reactivation of viral infections, and development of opportunistic infections. T-cell defects and thymic function are similar to that seen in congenital thymic aplasia.^{6,33} Barrier defects of the mucous membranes are critical for the pathogenesis of

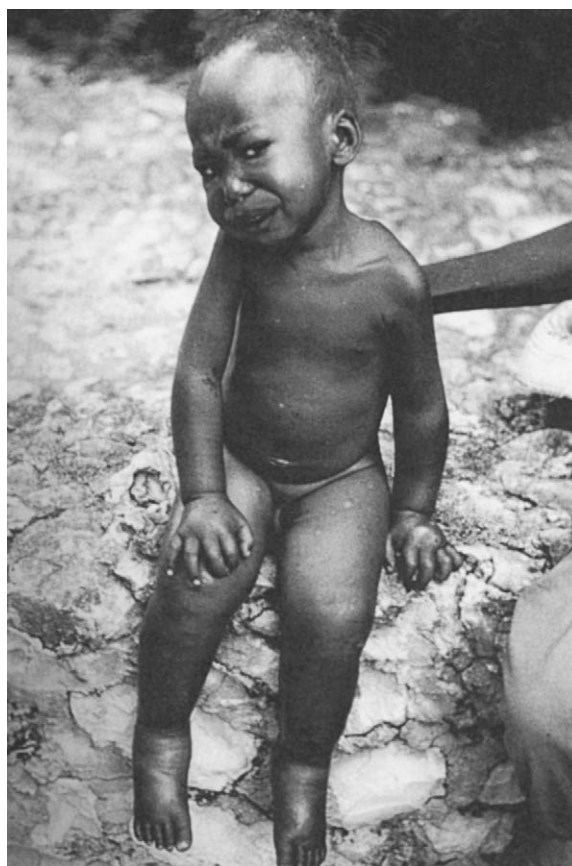


FIG 1. The malnourished child. This 4-year-old child from Deschappelles, Haiti, with kwashiorkor presents with marked skin infections and generalized edema. The sad expression and thinned hair are also frequently observed (courtesy of Dr Gretchen Berggren).

respiratory, gastrointestinal, and urinary tract infection. This is associated with changes in microbial flora.^{34,35} Nosocomial infections are common.³⁶ Reduced immune cell migration might be part of this picture. Experimental short-term dietary restriction impairs leukocyte exudation into local inflammatory sites in murine peritonitis by reducing CD11b/CD18 expression and production of the chemokine macrophage inflammatory protein 2.³⁷ The effects of PCM on the immune system are broad, involving all limbs of the immune system, in part because of complicating infections; these effects are summarized in Table I.

Cellular immune response is impaired and lymphocyte subsets are altered in PCM.³⁸ Preexisting infection will contribute to the effect of malnutrition. Tropical enteropathy often predates the onset of marasmus in Gambian children. This is characterized by a cell-mediated T_H1 response, leading to chronic enteropathy characterized by crypt hyperplasia, villous stunting, and high numbers of intraepithelial lymphocytes expressing CD25. T-cell numbers increase and B-cell numbers decrease with worsening nutrition, and mucosal cytokine production becomes biased toward a proinflammatory response.³⁹

TABLE I. Immune defects in nutrient deficiency

Clinical characteristics	Primary nutrient deficiency	Associated nutrient deficiency	Immune system	Immune response
Wasting, stunting, ↓ weight for height, growth (z score), nongenetic short stature	Protein calorie deficiency (marasmus)	Zinc, magnesium, selenium, copper, iron, vitamin A	Thymic atrophy, ↓ lymph nodes, tonsils, T cells, ↑ IgA, IgG is normal or ↑	↓ Skin test reactivity; ↓ cytokine response; might respond to vaccines; risk of bacterial, viral, parasitic, opportunistic infections
Moon face, edema, apathy, ↓ muscle mass, hepatomegaly, anemia	Protein deficiency (kwashiorkor)	Zinc, magnesium, selenium, copper, iron, vitamin A	Altered T-cell subsets, ↑ IgA, IgG is normal or ↑	↓ Skin test reactivity; ↓ cytokine response; might respond to vaccines; risk of bacterial, viral, parasitic, opportunistic infections
Diarrhea, skin lesions, infections, alopecia, poor wound healing	Zinc	Rarely iron, copper	Lymphopenia, thymic atrophy, altered T-cell subsets	↓ Skin test reactivity, ↓ cytokine response
Anemia, pallor, spoon-shaped nails, pica, infections	Iron	Zinc	T-cell defects, ↓ IgG levels, ↓ phagocytic activity	↓ Cytokine response, risk of parasitic and opportunistic <i>Candida</i> species infections
Neutropenia, anemia	Copper	↑ Zinc (might be causative)	Lymphopenia	Reduced IL-2 response
Muscle aches and pains, cardiomyopathy, infections	Selenium	Not reported	↓ Antioxidant defense	↑ Viral virulence
Xerophthalmia, keratomalacia, diarrhea and respiratory infections	Vitamin A	Zinc	Lymphopenia, ↓ mucosal barrier function	↓ T-cell response, especially TH2, ↓ phagocytic cell and NK cell function
Neurologic symptoms, atopic disease with ↑ IgE	Vitamin E	Selenium	↓ Antioxidant defense, ↑ IgE levels	↑ PGE ₂ production, ↑ viral virulence
Scurvy, purpura, petechiae, hyperkeratotic lesions, recurrent furunculosis, stress exercise	Vitamin C	Not reported	↓ Plasma glutathione	↓ Phagocyte function, risk of infections

PGE₂, Prostaglandin E₂.

These studies suggest that PCM is associated with reduction of regulatory immune responses in the mucosal microenvironment, potentially impairing the normal mechanisms of immune regulation and tolerance.

Serum immunoglobulin levels are normal or increased in most infants with PCM. The efficacy of T cell-dependent and T cell-independent vaccines in rural Gambian children with malnutrition and micronutrient deficiencies reveals a seasonal effect on hemoglobin levels, on micronutrients other than zinc and retinol, and on the response to vaccination.¹⁸ After adjusting for seasonality, age, and sex, no consistent associations were found between any of the measures of nutritional status and the effectiveness of seroconversion to the 23 valent pneumococcal capsular polysaccharide vaccine pneumovax and the rabies vaccine. Serum levels of IgA1, IgA2, and C4 tend to be higher in severely malnourished children than in normal children, whereas serum levels of C3 and the proportion of B cells are significantly lower.⁴⁰ In murine studies acute malnutrition leads to a pattern of increased TH2 cytokine production and increased IgE and IgG1 levels.⁴¹ In contrast, in the absence of infection, malnourished children show decreased serum IgE levels.⁴²

However, malnourished children with parasitic infections do show increased total IgE levels, but specific memory helper T-cell and specific IgE responses are reduced.⁴³

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is critically involved in the cause of the immunodeficiency of malnutrition. Leptin levels normally increase acutely during infection and inflammation.²⁵ However, serum leptin levels and insulin-like growth factor 1 are reduced in both marasmus and kwashiorkor.^{6,44} Thymic atrophy caused by PCM is associated with hormonal imbalance, loss of leptin, and an increase in serum glucocorticoid levels.⁶ Zinc deficiency also leads to increased glucocorticoid production.⁴⁵ Therefore nutrient deprivation leads to HPA activation and to increasing cortisol levels.⁴⁶ The relationship between plasma leptin, fat mass, and body mass index is disrupted in malnutrition and infection. Studies show no association between leptin levels, delayed-type hypersensitivity, secretory IgA, or immune response to vaccine.⁴⁷

PCM leads to increased susceptibility to infections and greater morbidity from infections.^{2,36} Hospitalized malnourished children require nutritional management for infection control.⁴⁸ Both gram-negative and gram-positive

bacterial infections are common. *Helicobacter pylori* infection is strongly associated with other enteric infections and chronic malnutrition in the postweaning period. *H pylori* infection might affect the homeostasis of different micronutrients, including iron, vitamin B₁₂, folic acid, alpha tocopherol, vitamin C, and β -carotene.⁴⁹ However *H pylori* is not a proved cause of persistent diarrhea or malnutrition in children.⁵⁰ In contrast, measles infection imposes severe metabolic demands on malnourished children. Compared with control subjects, measles-infected children have higher plasma cortisol level, plasma retinol levels, and IL-6 levels. Measles promotes a T_H1 to T_H2 cytokine shift, with depletion of plasma IL-12, a key cytokine in the development of cell-mediated immunity.⁵¹

The effects of primary malnutrition are reversible by refeeding. Renutrition studies in children show that innate immune functions, such as phagocytic function and microbicidal killing, and adaptive lymphocyte proliferative response improve in parallel with growth.⁵² Treatment of severely malnourished infants has shown that after refeeding, previously deficient phagocytosis, microbicidal activity, chemotaxis, and cell proliferation indices normalized along with anthropometric gains.⁵³

MICRONUTRIENT DEFICIENCIES

Micronutrient deficiencies are a major complication of PCM and promote infectious processes. Oxidative stress is worsened in infection if micronutrients are deficient. Vitamin A, β -carotene, folic acid, vitamin B₁₂, vitamin C, riboflavin, iron, zinc, and selenium have immunomodulating functions and influence both the susceptibility of the host to infectious diseases and the course and outcome of these diseases.⁵⁴ Many apparently healthy looking children have subclinical deficiencies of vitamin A, vitamin B₂, vitamin B₆, folate, and vitamin C.⁵⁵ Deficiencies of vitamin B₁₂, vitamin B₆, vitamin C, vitamin E, folate, niacin, or of the trace elements iron or zinc can cause DNA breaks, oxidative lesions, or both. In the US population, low intake (ie, less than 50% of the recommended daily allowance, which is sufficient to cause this level of effect) is common, ranging from 2% to more than 20%.⁵⁶ Premature infants require even more nutrient support because of their additional metabolic burden. Levels of selenium⁵⁷ and zinc⁵⁸ are often low, even when intake follows current guidelines. Human milk normally provides bioavailable micronutrients, such as zinc, as well as secretory immunoglobulin and growth factors.^{59,60} However, some maternal milk might be lacking in zinc, even when normal levels are found in serum, and in such cases babies might have a condition that is phenotypically identical with the inherited zinc malabsorption disorder acrodermatitis enteropathica (AE).⁶¹

Iron deficiency

Controversy about iron supplementation has continued over several decades because of concern that excess or inappropriate timing of iron repletion might promote

bacterial growth. Iron supplementation might adversely affect outcomes in individuals who present in the acute-phase response to infection, injury, or stress or who carry genes predisposing them to iron overload. Iron overload caused by blood transfusion is a serious complication of β -thalassemia because of organ toxicity. Incidence of infections in transfusion associated iron overload is fairly rare. Although reports of temporal relationship of transfusion to infection suggest such a correlation, cause-and-effect relationships have not been established.^{62,63} In hereditary hemochromatosis, a disorder of increased iron uptake, there is a paradoxical iron deficiency of macrophages, which might result in increased resistance to bacterial pathogens.⁶⁴

Iron chelation therapy of *Plasmodium falciparum* infection alleviates the clinical course of cerebral malaria in children. However, this appears to be due to enhanced generation of nitric oxide rather than to reduced iron availability to the parasite.⁶⁵ Iron supplementation has a significant and positive effect on iron status in anemia caused by malaria and no effect on the incidence of malarial infection.⁶⁶ Iron is a critical cofactor in immune function. Iron deficiency anemia in children is associated with reduced phagocytic activity and immunoglobulin levels.⁶⁷ Iron deficiency impairs the T-cell response and IL-2 production.⁶⁸

Zinc and copper deficiency

Zinc deficiency affects about one third of the world's population and is a frequent component of PCM.⁶⁹ Zinc deficiency is also a significant complication of IgA deficiency, fetal alcohol syndrome, sickle cell disease, enteritis, celiac disease, and many forms of diarrhea.^{5,54,70} Zinc is an essential cofactor for the activity of many enzymes, including thymic hormone.⁷¹ Deficiency leads to reduced T_H1 cytokines and thymic hormone activity⁷²⁻⁷⁴ and to lymphopenia.²⁰ Zinc supplementation improves pathogen-specific cell-mediated immunity in severely malnourished children.⁷⁵ Reprogramming of the immune system occurs with prolonged zinc deficiency, leading to activation of the HPA axis and chronic production of glucocorticoids that accelerate apoptosis among early T and B cells.⁴⁵ The autosomal recessive genetic defect of zinc absorption, AE, presents in infancy as skin lesions (acute dermatitis or hyperkeratotic plaques), diarrhea, alopecia, and increased incidence of infections caused by severe immune deficiency.⁷⁶ Immune defects range from severe thymic atrophy and profound lymphopenia to skin test anergy and loss of natural killer (NK) cell activity.⁷⁴ AE is centrally caused by mutations in SLC39A4, which encodes a ZIP zinc transporter protein. Increased zinc availability increases expression of zinc transporters. AE resolves with increased zinc supplementation.⁷⁷ Gestational zinc deficiency caused by an imbalance between intake and increased requirements is a common problem worldwide.¹² Maternal defects in zinc transport into milk can also cause infant zinc deficiency.⁶¹ Zinc-fortified formulas have been used to improve both linear growth and immunocompetence in infants with

PCM, as shown by improved skin tests, enhanced lymphoproliferative responses, and increased salivary IgA levels.⁷⁸ Preliminary data suggest a beneficial effect of prenatal maternal zinc supplementation on infants' neurobehavioral development and immune function.⁷⁹

Copper and zinc deficiency are common in children with hypoproteinemia and anemia, and this leads to reduced antioxidant function, as measured by superoxide dismutase activity.²⁸ Zinc competes with copper for gastrointestinal uptake, and increased zinc intake can induce copper deficiency, causing neutropenia.⁸⁰ The IL-2 response is reduced in copper deficiency.⁸¹ Serum copper or ceruloplasmin levels reflect the severity of malnutrition.⁸²

Selenium deficiency

Selenium deficiency can be a critical component of PCM in areas of the world with soil deficiency and is more severe in patients with kwashiorkor than in patients with marasmus.³⁰ Juvenile cardiomyopathy (Keshan disease) appears to involve both selenium deficiency and enteroviral infection, and related experimental studies suggest that this micronutrient deficiency enhances viral virulence.⁸³ Selenoproteins are an important component of the antioxidant host defense system affecting leukocyte and NK cell function.⁸⁴ A low selenium level is linked with increased viral virulence and progression in children with HIV infection.⁸⁵

Antioxidant vitamin deficiency

The antioxidant vitamins A, E, C, and β -carotene are cofactors in the immune response. Vitamin A has a broad range of immunologic effects, and vitamin A deficiency, which affects 140 million preschool children worldwide,⁸⁶ is associated with severity of many infections, including measles, rotavirus, and HIV.^{87,88} Low vitamin A levels might be prevalent in the primary immune deficiency disorder characterized by panhypogammaglobulinemia, common varied immunodeficiency disease. Low vitamin A levels in common varied immunodeficiency disease were associated with the occurrence of chronic bacterial infections and splenomegaly, as well as high neopterin levels. Vitamin A supplementation improved levels of serum IgA immunoglobulin and CD40 ligand-activated IgG and also led to reduced inflammatory cytokines.⁸⁹

Xerophthalmia is associated with childhood infections, such as measles, diarrhea, and respiratory tract infections, among hospitalized children in less developed countries,⁹⁰ and supplementation is beneficial.⁹¹ Respiratory infection and diarrhea can be signs of subclinical low vitamin A levels in children in impoverished environments.⁹² Reduced levels of serum transretinol are common in infants of HIV-1-infected mothers.⁹³ Vitamin A deficiency impairs mucosal barriers and diminishes the function of neutrophils, macrophages, and NK cells.⁹⁴ Intestinal barrier function in children is inversely correlated with serum retinol concentrations.⁹⁵ Experimental deficiency appears to cause functional disturbance of intestinal epithelium enzymes, producing diarrhea and increased bacterial translocation in gnotobiotic rats.⁹⁶

Vitamin A deficiency impairs both T_H1 - and T_H2 -mediated immune responses, although T_H2 responses seem to be principally affected.⁹⁷ This might explain why treatment with vitamin A reduces episodes of *P falciparum*-induced malaria.⁹⁸

Vitamin E is a strong antioxidant that can support monocyte/macrophage-mediated responses.^{99,100} Vitamin E influences T-cell function by downmodulating prostaglandin E_2 in elderly subjects.¹⁰¹ Emerging studies suggest improvement in eczema and reduced serum levels of IgE in atopic subjects.^{102,103} Current studies suggest that vitamin E deficiency might enhance virulence in viral infections.¹⁰⁴

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.¹⁰⁵ Ascorbate increases inducible nitric oxide synthetase production by macrophages activated by LPS¹⁰⁶ and also regulates the phagocytic process by decreasing free radical production and thus potentially reduces the severity of the endotoxin response.¹⁰⁷ Interesting new studies show that during stress exercise, contracting skeletal muscle is a major contributor to the exercise-induced increase of plasma IL-6 and that supplementation with vitamins C and E attenuates this response.¹⁰⁸

SECONDARY MALNUTRITION

When malnutrition presents in association with an underlying genetic disorder, chronic infection, or other illness that affect the metabolism, such as congenital heart disease, cystic fibrosis, or renal insufficiency, resolution cannot be obtained by nutritional means unless the underlying cause is treated. A more extensive discussion of secondary malnutrition is provided elsewhere.³ Parenteral nutrition might be required in some conditions, and this has been associated with nutrient deficiency and immune defects. However, a recent systematic review concluded that there are no consistent negative effects of long-term parenteral feeding on gut immune response in short bowel syndrome.¹⁰⁹ Other conditions, including low birth weight and intrauterine growth retardation, might have fundamental effects on the HPA axis. Increased plasma concentrations of growth hormone and leptin, lower concentrations of insulin-like growth factor 1 in early postnatal life, and increased insulin during subsequent growth in intrauterine growth retardation might affect immune mechanisms.¹¹⁰ Food intolerance, including food allergy, carbohydrate malabsorption, and gluten sensitivity, is increasingly common in children. The basis of this is unclear but might involve altered exposure to environmental antigens in early life.¹¹¹ Milk intolerance has recently been shown to be associated with failure to develop immune tolerance mediated by T-regulatory cells.¹¹²

Suboptimal levels of micronutrients are often found in children with inflammatory bowel disease, although with

the exception of iron and folate, it is unusual to discover symptoms attributable to these deficits.¹¹³ Both ulcerative colitis and Crohn's disease involve inflammation of the bowel and are chronic conditions. Current evidence suggests that this inflammation arises from an abnormal response to commensal bacterial antigens, suggesting abrogation of tolerance.^{114,115} Experimental evidence indicates that intestinal microorganisms produce intestinal inflammation in IL-10 knockout mice, and this is associated with an increased number of adherent clostridia and a decrease of lactobacilli and bifidobacteria. The inflammatory response in this model might be reduced by the addition of commensal lactobacilli organisms.¹¹⁶ Genetic variants of Nod2, an intracellular sensor of bacteria-derived muramyl dipeptide, appear to increase susceptibility to Crohn's disease. Nod2-deficient mice are susceptible to oral bacterial infection caused by loss of antimicrobial peptides in the gut.¹¹⁷ Introduction of a Nod2 variant into the mouse gene locus caused increased activation of nuclear factor κ B, leading to increased IL-1 β secretion, which might explain increased intestinal inflammation in response to bacteria in Crohn's disease.¹¹⁸

Obesity is a major nutritional disorder with adverse effects on growth and immune function caused by a maladaptive increase in the amount of energy stored as fat. Fatty acid composition of immune cells has a major regulatory effect on immune response.¹¹⁹ Obese adolescents with increased body mass index show altered T-lymphocyte subsets and increased TNF- α production.¹²⁰ Weight loss in obesity might be associated with improved immune function *in vitro*¹²¹ and decreased infections.¹²²

Alteration in leptin sensitivity and leptin signaling is implicated in eating disorders. Congenital leptin deficiency is a rare condition that is associated with severe obesity and hyperphagia accompanied by metabolic, neuroendocrine, and immune dysfunction.¹²³ The leptin receptor is expressed on mononuclear cells, and leptin stimulates the production of proinflammatory cytokines and enhances the production of T_H1-type cytokines.^{124,125} Leptin production is decreased in the subgroup of bulimic patients with a more chronic disease and with a greater severity of bingeing-vomiting behavior.¹²⁶

CHRONIC INFECTION

Proinflammatory cytokines initiated during the acute-phase response to infection act to elicit cellular responses throughout the body, and nutrients are lost during any generalized febrile infections. This response is affected by malnutrition.¹²⁷⁻¹²⁹ Energy expenditure increases at the same time that the infected host experiences a decrease in intake, and diarrhea might result in decreased intestinal absorption of nutrients.⁴

HIV

Malnutrition continues to be a significant problem in pediatric HIV infection. Studies show that micronutrient

impairment is causally associated with the course of HIV infection and immune dysfunction. Deficiencies of micronutrients are common.⁸⁵ Nutritional interventions might restore intestinal absorption and increase CD4 cell numbers.¹³⁰ Selenium deficiency increases the virulence of HIV and enhancing disease progression. Selenium supplementation reduces high levels of IL-8 and TNF- α , which have been associated with neurologic damage, Kaposi sarcoma, wasting syndrome, and increased viral replication.¹³¹ Selenium status also appears to affect the pathogenesis of mycobacterial disease.¹³² Vitamin A might increase the risk of HIV-1 transmission through breast milk. In contrast, multivitamin supplementation of breast-feeding mothers with vitamins B, C, and E reduces child mortality and HIV-1 transmission through breast-feeding among immunologically and nutritionally compromised women.¹³³ Supplementation in children with HIV improves overall health.^{88,134} Clinical benefit of supplementation with some micronutrients might be measurable in the presence of preexisting deficiency. As treatment and prophylactic regimens improve, the current nutritional problems of HIV-infected children in developed countries include truncal obesity and insulin resistance in addition to malnutrition.¹³⁵

Parasitic infections

Parasitic infections cause malnutrition, impair the host immune response, and are affected by host nutrition and immunity. Intestinal hookworm causes significant anemia.¹³⁶ 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* might cause severe anemia in an infant that is difficult to correct with iron supplementation alone. Heavy infections with *Ascaris* species might result in malabsorption, mild anemia, and wasting. The worm metabolizes vitamin A, and heavy infections have been associated with vitamin A deficiency.

Malaria causes the most serious nutritional consequences of any major parasite. It causes hypochromic microcytic anemia. This is not associated with iron deficiency, except in the case of hemoglobinuria that occurs with blackwater fever (*P falciparum*). Erythroid recovery from malaria requires increased amounts of folate. The malaria parasite infects the placenta of pregnant women, compromising blood flow to the fetus and increasing the risk of low birth weight among infants in developing countries.

Zinc deficiency impairs immune response to intestinal nematode infections at both the systemic and intestinal levels.¹³⁷ Infection also alters host nutrition because diarrhea promotes zinc loss. Giardiasis increases the serologic levels of copper, whereas zinc and iron levels are decreased because of malabsorption. CD4⁺ T_H2 cells are critical for host protection, whereas the T_H1 response actually inhibits protective immunity to nematode infection. IL-4, a T_H2 cytokine, is required for protection and can also limit the severity of infection. Protein malnutrition

might increase the survival of nematode parasites by decreasing gut-associated IL-4 (T_H2) and increasing IFN- γ (T_H1), leading to reduced intestinal and systemic T_H2 effector responses.¹³⁷

SUMMARY

PCM is the major common cause of secondary immune deficiency in the world. In most cases PCM involves both protein calorie and micronutrient deficiency of vitamin A, vitamin E, vitamin B₆, folate, zinc, iron, copper, and selenium. PCM is defined as marasmus, a chronic wasting condition, or kwashiorkor, which is distinguished by edema and anemia. Marasmus occurs with caloric insufficiency, whereas kwashiorkor develops from protein deficiency. PCM leads to atrophy of lymphoid organs, profound T-lymphocyte deficiency, and increased susceptibility to bacterial and viral pathogens and opportunistic infections. Barrier defects of the mucous membranes are caused by immune deficiency and altered immune regulation, and cellular trafficking also involve changes in microbial flora. Thymic atrophy caused by PCM is associated with hormonal imbalance, loss of leptin, and increase in circulating cortisol levels. Oxidative stress is worsened in infection if micronutrients are deficient. Deficiencies of the vitamins B₁₂, vitamin B₆, vitamin C, vitamin E, folate, niacin, or of the trace elements iron or zinc might cause DNA breaks, oxidative lesions, or both. Zinc, copper, iron, and selenium are essential for normal immune response. Vitamin A deficiency impairs mucosal barriers and diminishes the function of neutrophils, macrophages, and NK cells. Secondary malnutrition also leads to continuing immune deficiency but unlike PCM cannot be treated with nutritional support alone.

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Correction

With regard to the March 2005 Current Reviews article entitled "Insect allergy and venom immunotherapy: A model and a mystery" (2005;115:439-47): Reference is made on page 440 to a yellow jacket in the Journal's cover illustration. The editorial staff made a decision to use an image of a wasp (*Polistes exclamans*) instead of a yellow jacket, and because the author, David B. K. Golden, was not made aware of this change he had no opportunity to revise his article so as to refer to the insect in the illustration as a wasp. Our apologies to Dr Golden.

An image of the yellow jacket, *Vespula maculifrons*, appears below.

