Synergism of nutrition, infection, and immunity: an overview¹–³

Nevin S Scrimshaw and John Paul SanGiovanni

ABSTRACT Infections, no matter how mild, have adverse effects on nutritional status. The significance of these effects depends on the previous nutritional status of the individual, the nature and duration of the infection, and the diet during the recovery period. Conversely, almost any nutrient deficiency, if sufficiently severe, will impair resistance to infection. Iron deficiency and protein-energy malnutrition, both highly prevalent, have the greatest public health importance in this regard. Remarkable advances in immunology of recent decades have increased insights into the mechanisms responsible for the effects of infection. These include impaired antibody formation; loss of delayed cutaneous hypersensitivity; reduced immunoglobulin concentrations; decreased thymic and splenic lymphocytes; reduced complement formation, secretory immunoglobulin A, and interferon; and lower T cells and T cell subsets (helper, suppressor-cytotoxic, and natural killer cells) and interleukin 2 receptors. The effects observed with single or multiple nutrient deficiencies are due to some combination of these responses. In general, cell-mediated and nonspecific immunity are more sensitive than humoral immunity.

KEY WORDS Nutrition and infection, nutrition and immunity, vitamins and minerals, minerals and immunity

INTRODUCTION

It is appropriate to begin a keynote lecture with a historical introduction. The 1968 WHO monograph Interactions of Nutrition and Infection (1) suggested for the first time that the relation between infection and malnutrition is synergistic. The monograph brought together extensive evidence for both the adverse effect of infections on nutritional status and the increased susceptibility to infection of malnourished individuals. Its thesis was that each worsened the other and that the biological effects of malnutrition and infection combined were greater than the sum of the two for this reason.

The monograph also tried to identify the mechanisms involved in this interaction. Its documentation of the ways in which infection worsens nutritional status was comprehensive and relatively complete even by today’s standards. However, its review of the ways in which malnutrition can affect resistance to infection was written before the modern explosion in immunologic research. This conference provides an opportunity to present and interpret the rapidly increasing knowledge of interactions between nutrient deficiencies and immune status.

I summarize the multiple ways in which infections can affect nutritional status and then give an overview of the possible mechanisms for the reciprocal relation between malnutrition and reduced resistance to infection. These include the following.

Anorexia

Nitrogen balance studies disrupted by intercurrent infections or even immunizations reveal consistent decreases in food intake. This is a factor in precipitating clinically evident deficiencies of any nutrient that is already borderline or deficient in the individual.

Cultural and therapeutic practices

Withdrawal of food from individuals with fever, diarrhea, or other symptoms of infection is an almost universal practice that exacerbates the effect of anorexia. In field studies it is not possible to separate the effects of anorexia from those of deliberate withdrawal of food for cultural reasons, but the combined effects can be devastating. In Matlab, Bangladesh, food intakes as judged from dietary energy were > 40% reduced in children aged < 5 y during the acute stage of diarrhea compared with after recovery (2). In Peru, energy intakes decreased between 10% and 86% in breast-fed children with diarrhea (3).

Decreased intestinal absorption

In studies by the Institute of Nutrition of Central America of Panama, protein absorption was generally reduced 10–30% and sometimes as much as 40% in children with diarrhea (4). In Bangladesh, absorption during diarrhea caused by rotavirus averaged 43% for nitrogen, 42% for fat, 74% for carbohydrate, and 55% for total energy (5). Corresponding values for diarrhea caused by enteropathogenic Escherichia coli and Shigella were slightly higher.

The range of infections associated with malabsorption is wide. Included are bacterial, viral, and protozoan enteritides.

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and intestinal helminths (6). Vitamin A malabsorption also occurs during systemic febrile illnesses. Sivakumar and Reddy (7) reported that in children with acute diarrhea and respiratory infections only 30–70% of ingested vitamin A is absorbed.

Catabolic losses

A catabolic response occurs with all infections even when they are subclinical and not accompanied by fever (8–12). Under the stimulus of the release of interleukin 1 by leukocytes, endocrine changes are initiated that lead to the mobilization of amino acids from the periphery, primarily from skeletal muscle (8). The amino acids are used for gluconeogenesis in the liver and the nitrogen released is excreted in urine.

Protein

To describe the effect of infection on protein losses, Powanda (13) summarized data from a wide variety of acute infectious diseases by adding the total nitrogen losses and dividing them by the number of days over which these losses occurred. For all infections, the average loss of 0.6 g protein·kg⁻¹·d⁻¹ is equal to the mean estimated total protein requirement for adults. Diseases associated with diarrhea or dysentery produced an average loss of 0.9 g protein·kg⁻¹·d⁻¹. Higher losses were observed with typhoid fever and other severe infections, reaching 1.2 g protein·kg⁻¹·d⁻¹ (13).

With use of urinary 3-methylhistidine as a measure of muscle protein catabolism in septic patients, losses from 12 to 30 mg/d were detected during the peak fever response (14). By this measure, the average additional loss in the urine during sepsis was equivalent to 1.14 g protein·kg⁻¹·d⁻¹. Such calculations are underestimates of the metabolic cost of infections, however, because they do not include energy expended for the multiple anabolic responses described below.

Lipids

Infections affect plasma lipids but the changes are highly variable and depend on the duration and severity of infection, the degree of fever, and age. Effects include changes in triacylglycerol, fatty acids, ketone bodies, and the products of fatty acids partially oxidized in the liver.

Carbohydrates

The catabolic responses described above have as a principal function the provision of amino acid substrates for gluconeogenesis. Thus, a continual conversion of alanine carbon to glucose carbon occurs with acute infection, even when exogenous carbohydrate is adequate. It appears to be the rate of release of glycogenic amino acid substrates from peripheral tissues that determines the rate of hepatic gluconeogenesis. All of the hormones that regulate carbohydrate metabolism participate in host responses to infection. Several groups have documented an increased fasting concentration of both glucagon and insulin in serum. Despite the initial stimulation of gluconeogenesis, the body may eventually become severely hypoglycemic. Lethal hypoglycemia can develop in septic neonates with severe viral infections of the liver such as fulminating hepatitis or, as shown in monkeys, yellow fever.

Energy

The energy cost of depositing 1 g protein has been estimated to be 100 kJ (24 kcal) or ≃ 25 kJ (6 kcal) of total weight gain. If this figure is applied to the observed protein losses summarized above, calculated average energy losses from this source alone would be between 17 and 21 kJ·kg⁻¹·d⁻¹ (between 4 and 5 kcal·kg⁻¹·d⁻¹). This amount seems small but it represents 14–29% of the requirements of a 1-7-year-old child. Increased protein loss during infections, estimated from increased urinary 3-methylhistidine excretion, is the energy equivalent of ≃ 29 kJ·kg⁻¹·d⁻¹ (≈ 7 kcal·kg⁻¹·d⁻¹). Jackson et al (15) in Jamaica measured the energy cost of growth of children recovering from protein-energy malnutrition and reported a range of weight gain of 17–21 kJ/g (4–5 kcal/g) with 40% of this considered to be fat tissue and 60% protein tissue. They estimate the energy cost of synthesizing 1 g lost protein to be 31 kJ (7.5 kcal) and that for replacing 1 g fat to be 48.5 kJ (11.6 kcal).

Vitamin A

The capacity of infections to precipitate xerophthalmia and keratomalacia in individuals already marginally deficient is well established and the effect is particularly severe with measles and also noted for chickenpox. A significant drop in serum vitamin A concentrations has been observed in children with acute respiratory infection, gastroenteritis, and measles, with concentrations returning to normal after recovery. Vitamin A blood concentrations also have been reported to be reduced in pneumonia, rheumatoid arthritis, acute tonsillitis, and infectious hepatitis. Lower serum carotene and vitamin A concentrations also have been found with hookworm disease.

Ascorbic acid

Ascorbic acid concentrations decrease in plasma and increase in the urine of infected individuals compared with noninfected persons living under comparable conditions. This is seen even with vaccination against smallpox and measles and for the common cold.

B vitamins

The classic nutritional diseases of beriberi and pellagra were known to be precipitated in vulnerable individuals by a variety of infections. Riboflavin status is also adversely affected by infection. Beisel et al (16) showed marked increases in riboflavin excretion with sandfly fever in well-nourished male volunteers.

Iron

One metabolic consequence of infection is a decrease in serum iron because of its being sequestered in the reticuloendothelial system. In addition, lactoferrin, with a higher iron binding capacity than bacterial siderophores, is released by phagocytes. The net effect is to deprive the infectious agent of iron for its replication and inhibit the spread of infection.

Other minerals

Infections decrease both serum copper and zinc. Careful metabolic studies by Castillo-Duran et al (17) documented the effect of diarrhea on zinc and copper status. Metabolic balances of these minerals were strongly negative during periods of
acute diarrhea. These losses cannot be predicted from serum concentrations because copper concentrations often increase during infection as a result of stimulation of the hepatic production of ceruloplasmin. Note that in this study serum copper concentrations were significantly lower in subjects with diarrhea than in control subjects. Conversely, plasma zinc concentrations often decline during acute infections because of an internal redistribution of the metal to the liver. The reduced retention of zinc during diarrhea thus interacts with the redistribution influence of the infection.

Anabolic losses
During infection, amino acids are diverted from normal pathways for the synthesis of immunoglobulins, lymphokines, C-reactive proteins, and a variety of other proteins including key liver enzymes (10).

Fever
Fever increases the basal metabolic rate 13% for each 1 °C. During a period of high fever, metabolism may increase by nearly one-third (18). Additional nitrogen and amino acids are lost in sweat.

Additional intestinal losses
Protein-losing enteropathy has been described for measles and diarrhea, especially when due to shigellosis. In studies by the International Center for Diarrheal Disease Research–Bangladesh, nearly two-thirds of patients with enterotoxigenic E. coli and 40% of those with rotavirus diarrhea had excessive losses of protein in feces. In patients with shigellosis, between 100 and 500 mL serum was lost with feces each day as a result of protein-losing enteropathy (4).

Bleeding into the intestine from Schistosoma mansoni, or hookworm, also results in significant losses of iron and energy. Each adult hookworm causes the loss of ~4.2 kJ/d (1 kcal/d) and 0.03–0.26 g blood depending on the species (19). Less than one-half of iron lost in this way is reabsorbed. Chronic urinary blood loss with Schistosoma hematobium also increases iron requirements, as does the sequestering of iron pigment by the reticuloendothelial system in malaria.

RELATION BETWEEN NUTRITION AND IMMUNITY
Reasons for malnutrition are multiple and complex, but, as reviewed above, infection is a common precipitating factor. Ironically, malnutrition is also a major factor in the occurrence of infection and the two interact, in many cases, making each other worse. The striking decrease in infectious disease morbidity in preschool children in Tzozontepec, Mexico, given additional milk is shown in Figure 1 (20).

To complete the overview of this synergistic interaction, the remainder of this paper summarizes the mechanisms responsible for decreased resistance to infection and the specific nutrient deficiencies that affect them. These potential mechanisms include interference with the production of humoral antibodies and of mucosal secretory antibodies, cell-mediated immunity, bactericidal capacity of phagocytes, complement formation, numbers of thymus-dependent T lymphocytes and T cell subsets (helper, suppressor-cytotoxic, and natural killer cells), and nonspecific defense mechanisms. These nonspecific defense mechanisms include intestinal flora; anatomical barriers (skin, mucosa, and epithelium); secretory substances such as lysozymes, mucus, and gastric acid; the febrile response; endocrine changes; and binding of serum and tissue iron.

Antimicrobial systems in the neutrophil, all of which are potentially affected by malnutrition, are listed in Table 1. These include both oxygen-dependent systems, such as those responsible for the respiratory burst, and oxygen-independent systems, such as lactoferrin, lysozymes, hydrolase, and proteases. Some of the still fragmentary evidence for the role of specific nutrients in each of the mechanisms is summarized below.

The 1968 WHO monograph on nutrition and infection (1) summarized conclusions from experimental animal and human

**FIGURE 1.** Percentage of days sick per semester for children in the maternal supplementation and complementary feeding group (solid bars) compared with children breast-fed by unsupplemented mothers who received no complementary food from the program (dashed bars). Values are for the first 30 wk of the supplementation program. *t* ± SD. Reproduced with permission from the International Nutrition Foundation (20).


TABLE 1
Antimicrobial systems in the neutrophil

<table>
<thead>
<tr>
<th>Oxygen dependent</th>
<th>MPO dependent</th>
<th>MPO, halide, H₂O₂, MPO independent, H₂O₂, Hydroxyl radical (OH)</th>
<th>Singlet oxygen (¹O₂)</th>
<th>Superoxide anion (O₂⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid environment</td>
<td>Cationic proteins</td>
<td>Lysozyme</td>
<td>Lysosomal hydrolases</td>
<td>Neutral proteases</td>
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</tbody>
</table>

1 MPO, myeloperoxidase. Table adapted from Stinnert (21).

studies then available. Assembled for the first time, 325 of these studies provided evidence that many infections were increased in prevalence or severity by specific nutritional deficiencies. However, 93 studies, almost all of them in experimental animals, indicated that it was possible to produce deficiencies that were sufficiently severe enough to affect replication of the infectious agent. The monograph introduced the terms synergism to describe the former and antagonism to characterize the latter.

At the time of this 1968 monograph there was already extensive evidence, mainly from studies in experimental animals, of the depressing effects of a variety of nutrient deficiencies on antibody formation and leucocyte function. There was no corresponding body of information for effects on cell-mediated immunity. There are, of course, now many more published research studies and a series of books on the subject including ones by Stinnert (21), the Nestlé Foundation (22), Gershwin et al (23), Bendich and Chandra (24), Chandra (25), and Cunningham-Rundles (26), as well as several reviews (12, 27–32). In addition, the quarterly Journal of Nutritional Immunology began publication in 1992. However, the overall conclusions of the 1968 tabulation have not changed.

The most important advances are 1) many more studies in human subjects and the strengthened evidence for the damaging effects on immunity of iron and protein-energy deficiencies in children and 2) a veritable explosion in the sophistication of immunologic studies, including studies of the role of cytokines. Much of the evidence relates to deficiencies of specific nutrients, some of which are summarized below. Where specific references are not given they can be found in the books and reviews listed above.

Protein

More than 100 studies in experimental animals alone have shown the adverse effects of protein deficiency on immunity and the clinical and public health significance of these studies has been confirmed by dozens of clinical and field studies. It is not surprising that protein deficiency is so consistently observed to interfere with resistance to infection because most immune mechanisms are dependent on cell replication or the production of active protein compounds. Because protein can-
amino acids, particularly arginine (76), to the diet will improve the immune response. Arginine administered in clinical studies enhanced phagocytes of alveolar macrophages (77), depressed T suppressor cells, and stimulated T helper cells (76). The "nonessential" amino acid glutamine is necessary for, and has a high flux in, lymphocytes and other rapidly growing cells. This may be a factor in the diminished integrity of the immune system with the reduced protein turnover associated with low protein intakes. Leucine administered to sheep decreased antibody response (78).

Vitamin A

Experimental animals made deficient in vitamin A generally have increased susceptibility to infection. There have now been several studies, eight of which are summarized in Table 2, of the effect of vitamin A administration to preschool children. In six of these studies, large drops in mortality ranging from 30% to 50% were observed. Two of the studies showed no effect, perhaps because other deficiencies were limiting. Surprisingly, morbidity was not affected (88).

Vitamin A–deficient experimental animals have decreased thymus and spleen sizes, reduced natural killer cell activity, lower production of interferon, impaired delayed cutaneous hypersensitivity, less effective fixed fat macrophage activity, and lower lymphocyte response to stimulation by mitogens (74). Phagocytotic activity may also be affected. However, there is no understanding of how vitamin A deficiency exerts its effect on human resistance (23).

Vitamin A is essential for maintaining epidermal and mucosal integrity but this does not appear to be compromised in the populations studied. Most clinical studies find no effects on T cell function (89). Dietary vitamin A increased T cell mitogenesis in lung patients and reversed postoperative immunosuppression (74). High intakes of vitamin A are mixed in their effects, enhancing some immune infections and suppressing others (74).

β-Carotene

β-Carotene in vivo can stimulate rat lymphocyte mitogenesis (90) and increase human natural killer cell (91) and T helper cell (92) numbers. The administration of β-carotene to elderly humans increased the ratio of CD4 to CD8 but had no effect on natural killer cells, virgin T cells, memory T cells, or cytotoxic T cells (93). β-Carotene added in vitro to human lymphatic cultures stimulated natural killer cell activity but did not affect other T cell subsets (94).

B vitamins

Pyridoxine deficiency has been associated with reduced cell-mediated immunity in both experimental animals and in humans. Hodges et al (95) reported that subjects given a diet deficient in pantothenate had a normal response to typhoid antigen but a reduced response to tetanus toxoid. With pyridoxine deficiency, formation of antibodies against tetanus and typhoid was slightly reduced (96). With combined pantothenate and pyridoxine deficiency, the immunologic response was almost completely inhibited but became excellent when these vitamins were restored to the diet (97).

Folic acid and vitamin B-12 are so essential to cellular replication that the finding that experimental deficiencies of

![Figure 2](https://academic.oup.com/ajcn/article-abstract/66/2/464S/4655772)
these vitamins interfere with both antibody formation and replication of stimulated leukocytes was expected. The vitamins are also associated with thymic atrophy, as is choline deficiency. In folic acid deficiency anemia, cell-mediated immunity is depressed (98).

Vitamin C

The reported immunologic and related consequences of ascorbic acid deficiency are listed in Table 3. Decreased neutrophil function, impaired delayed cutaneous hypersensitivity, and abnormal serum complement concentrations have been documented in studies in both experimental animals and human subjects. Reduced phagocytic response and killing power as well as reduced antibody response have been described in clinical studies. Studies of experimentally induced scurvy in humans found normal lymphocyte stimulation response in vitro to T cell mitogens and no change in lymphocyte subsets (111). There is not conclusive evidence to support the hypothesis that ascorbic acid deficiency in humans leads to either altered cell-mediated or humoral immunity. The many claims of a favorable effect on infection of massive doses of vitamin C have not been confirmed in studies with acceptable experimental designs and are not reviewed here.

Vitamin D

Vitamin D serves as both an immunoregulatory hormone and a lymphocyte differentiation hormone in addition to its role in mineral homeostasis.

Vitamin E

Alterations in immunity reported with vitamin E deficiency are listed in Table 4. Reduced lymphocyte and leukocyte killing power has been shown in humans as well as in experimental animals. In animals it was shown to interfere with antibody formation, plaque-forming cells, and other aspects of cell-mediated immunity. Vitamin E supplementation has been reported to enhance both humoral and cell-mediated immunity and to augment the efficacy of phagocytosis in experimental and farm animals and humans (23, 121, 129, 130). Vitamin E is one of the few nutrients for which supplementation at higher than recommended levels has been shown to enhance immune response and resistance to disease (121).

Iron

Iron deficiency is the most widespread nutrient deficiency in the world today and in field studies is consistently associated with increased morbidity from infectious diseases. Moreover, iron supplementation of iron-deficient populations results in decreased frequency of infectious episodes. The reported effects of iron deficiency on immune function are listed in Table 5. Mechanisms clearly identified are impaired phagocytic killing power, less response to lymphocyte stimulation, fewer natural killer cells associated with reduced interferon production, and depressed delayed cutaneous hypersensitivity. Apparently B cell and antibody formation are not affected. Bryan and Stone (147) provided an extensive review and analysis of the immunologically related properties of the iron molecule.

One of the most revealing animal studies is one conducted by Baggs and Miller (144), who found more viable intracellular and extracellular bacteria in the macrophages and intestinal walls of iron-deficient rats with experimental salmonellosis than in iron-replete animals. This was paralleled by the concentrations in the intestinal wall of the iron-containing enzyme myeloperoxidase, which mediates the iodination of proteins and the formation of hydrogen peroxide to kill microorganisms within the cell.

Chandra et al (145) showed a relation in Indian children between hemoglobin status and the capacity of lymphocytes to react to antigenic stimulation (Figure 3, top). He also showed the reduced capacity of phagocytes from malnourished Indian children to produce a respiratory burst (Figure 3, bottom) and hence a decrease in phagocytic killing power (Figure 3, middle) (145). There is extensive evidence for a direct relation between iron status and plasma T lymphocyte concentrations (67, 147). Impaired delayed cutaneous hypersensitivity to several ubiquitous antigens has also been described in iron-deficient children (67).

Iron overload and infection

Any discussion of the effect of dietary iron on immunity is incomplete without discussion of the biological mechanisms for withholding iron from invading organisms (148). Iron is needed for a wide variety of biochemical functions not only by the host but also by the infectious agent (149). Transferrin is found not only in blood but in all body fluids and is the normal mechanism for withholding iron from the infectious agent, as is lactoferrin. Conalbumin and lactoferrin have stronger iron binding properties than do most bacterial siderophores and are normally highly unsaturated.

Ferritin is the storage form of iron and as ferritin molecules become saturated with iron, some is metabolized to the inert intracellular ferric ion, hemosiderin. When molecules of lactoferrin become 40% saturated with iron, they are assimilated by macrophages that have been attracted to the site of infection.
and much of the iron is incorporated into ferritin. Ferritin functions as an iron-withholding rather than as an iron-transport agent.

Lactoferrin, known to be released during degranulation of leukocytes in aseptic areas, is a major component of human milk and resists proteolytic destruction in the gastrointestinal tract. It is not difficult to show in vitro the protective effect of lactoferrin. In an iron-deficient host with reduced immune function, lack of available iron for agent replication is protective. Baggs and Miller (144) found that in rats exposed to a standard dose of Salmonella, a diet lacking in iron is almost as protective as one meeting iron needs.

When individuals whose resistance to infection is compromised by iron deficiency are given parenteral iron or large doses of oral iron, a disastrous exacerbation of the infection and death may occur (150, 151). This happens because the agent is supplied with iron for replication before the host immune system has had time to recover. However, in field studies, supplementation of poorly nourished adults with physiologic amounts of up to 100 mg Fe/d and proportionately less for children, consistently results in decreased morbidity from infectious disease. It is important to recognize that there is a fairly large range of iron intakes over which the immune system can function normally.

Zinc deficiency

Zinc is a ubiquitous trace metal essential to the development and maintenance of the immune system and that influences both lymphocyte and phagocytic cell functions (152-155). More than 100 metalloenzymes have been identified that are zinc dependent. It is not surprising, therefore, that experimental zinc deficiency in animals is associated with the wide range of immunologically related consequences listed in Table 6.

These include extensive changes in T cell–related indexes. In the genetic disease acrodynatosis enteropathica—characterized by reduced intestinal zinc absorption—thymic atrophy, impaired lymphocytosis, and impaired response to stimulation are observed. However, unlike the situation for iron, there is no evidence that zinc deficiency in the underprivileged human populations of developing countries is severe enough to affect immunity. Nevertheless, the number of publications reporting the effects of experimental zinc deficiency on immunity outnumber those on iron by a ratio of 20 to 1. Excessive zinc intakes also impair immune responses (201).

Other mineral deficiencies

The immune effects of copper deficiency in experimental animals are listed in Table 7. They include both B cell– and T cell–related deficiencies. Impaired antibody formation, inflammatory response, phagocytic killing power, and lymphocyte stimulation responses, as well as thymic atrophy, have been well documented. The only clinical relevance of these observations is to children with Menkes syndrome, a rare congenital disease resulting in copper deficiency. Among its symptoms are increased bacterial infections, diarrhea, and bronchopneumonia. Note that anemia and reduced serum iron are characteristics of copper deficiency in rats that are not corrected by iron administration.

Magnesium participates in all major metabolic pathways and is an obligate cofactor for DNA synthesis (216). The immune effects of magnesium deficiency in experimental animals are listed in Table 8. Effects include the same range

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**Table 4**

<table>
<thead>
<tr>
<th>Decreased immune function</th>
<th>Animal</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral response, B cell function</td>
<td>Mice (112–115), rats (116)</td>
<td>Severe vitamin E deficiency (120, 121); premature infants respond to vitamin E supplementation (122)</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Mice (113)</td>
<td>Severe vitamin E deficiency (120, 121), vitamin E-deficient patients with tropical sprue (123)</td>
</tr>
<tr>
<td>T lymphocyte response</td>
<td>Mice (114, 115), rats (116), pigs (117), sheep (118), dogs (119)</td>
<td>Severe vitamin E deficiency (120, 121), glutathionedeficient neonates (127)</td>
</tr>
<tr>
<td>Delayed cutaneous hypersensitivity</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Phagocytic function</td>
<td>Mice (115), rats (124–126), pigs (117)</td>
<td>Severe vitamin E deficiency (120, 121), glutathionedeficient neonates (127)</td>
</tr>
<tr>
<td>Hemagglutination titers</td>
<td>Mice (112, 113)</td>
<td></td>
</tr>
<tr>
<td>Cytokine or lymphokine function or production</td>
<td>Rats (128)</td>
<td>Severe vitamin E deficiency (120, 121)</td>
</tr>
</tbody>
</table>

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**Table 5**

<table>
<thead>
<tr>
<th>Decreased immune function</th>
<th>Animal</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral response, B cell function</td>
<td>Rats (131, 132)</td>
<td>(131, 133, 134)</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Rats (131)</td>
<td></td>
</tr>
<tr>
<td>Thymic structure or function</td>
<td>Rats (135–137)</td>
<td></td>
</tr>
<tr>
<td>T lymphocyte response</td>
<td>Mice (138)</td>
<td>(61, 67, 133, 134, 139–142)</td>
</tr>
<tr>
<td>Delayed cutaneous hypersensitivity</td>
<td>—</td>
<td>(67, 141, 142)</td>
</tr>
<tr>
<td>Phagocytic function</td>
<td>Rats (143)</td>
<td></td>
</tr>
<tr>
<td>Killing power</td>
<td>Rats (144)</td>
<td>(145)</td>
</tr>
<tr>
<td>Cytokine or lymphokine function or production</td>
<td>Rats (146)</td>
<td></td>
</tr>
</tbody>
</table>
of altered T and B cell functions as described for copper and zinc deficiencies. For these minerals, there is no evidence of any public health significance to these observations because they have been limited to experimental animals. Selenium deficiency can also affect all components of the immune system (228).

**Overnutrition and infection**

Definitive studies on the effects of overnutrition on immune system function in humans are lacking. Lower respiratory tract infections have been reported to be higher in obese than in nonobese infants (229). Overfed and obese beagle dogs, chal-

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**TABLE 6**

Zinc deficiency causes the following decreases in immune function

<table>
<thead>
<tr>
<th>Decreased immune function</th>
<th>Animal</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral response, B cell function</td>
<td>Rodents (156), rats (157)</td>
<td>—</td>
</tr>
<tr>
<td>T cell–dependent antigens (SRBC)</td>
<td>Mice (158–168)</td>
<td>—</td>
</tr>
<tr>
<td>T cell–independent antigens (dextran)</td>
<td>Mice (161, 166, 167, 169)</td>
<td>—</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Mice (163, 164, 166, 168, 170)</td>
<td>(171)</td>
</tr>
<tr>
<td>Cell-mediated immunity functions</td>
<td>Mice (158, 168), rats (186)</td>
<td>(184)</td>
</tr>
<tr>
<td>Delayed cutaneous hypersensitivity</td>
<td>Mice (158, 169, 170, 193, 194)</td>
<td>(169, 171, 183, 185)</td>
</tr>
<tr>
<td>Phagocytic function</td>
<td>Mice (169, 187, 194–197)</td>
<td>(199)</td>
</tr>
<tr>
<td>Killing power</td>
<td>Mice (195, 197, 198)</td>
<td>—</td>
</tr>
<tr>
<td>Cytokine or lymphokine function or production</td>
<td>Mice (165), rats (186, 193)</td>
<td>(200)</td>
</tr>
</tbody>
</table>

*SRBC, sheep red blood cells.*
TABLE 7
Copper deficiency causes the following decreases in immune function

<table>
<thead>
<tr>
<th>Decreased immune function</th>
<th>Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral response, B cell function</td>
<td>Rodents (202), mice (203–206), rats (207, 208)</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Mice (204)</td>
</tr>
<tr>
<td>Thyric structure</td>
<td>Mice (202)</td>
</tr>
<tr>
<td>Cell-mediated immunity functions</td>
<td>Rodents (202), mice (187, 203, 206, 210), rats (211, 212)</td>
</tr>
<tr>
<td>T lymphocyte response</td>
<td>Mice (202, 203), rats (212, 213), sheep (214), cattle (214, 215)</td>
</tr>
<tr>
<td>Phagocytic function</td>
<td>Mice (204)</td>
</tr>
<tr>
<td>Cytokine or lymphokine function or production</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 8
Magnesium deficiency causes the following decreases in immune function

<table>
<thead>
<tr>
<th>Decreased immune function</th>
<th>Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral response, B cell function</td>
<td>Mice (217, 218), rats (219–221)</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Rats (220), mice (218)</td>
</tr>
<tr>
<td>Cell-mediated immunity functions</td>
<td>Rodents (221)</td>
</tr>
<tr>
<td>T lymphocyte response</td>
<td>Mice (187, 221, 222), rats (223, 224)</td>
</tr>
<tr>
<td>Cytotoxic T cells</td>
<td>Mice (222, 225–227)</td>
</tr>
<tr>
<td>Phagocytic function</td>
<td>Mice (187), rats (223, 224)</td>
</tr>
<tr>
<td>Cytokine or lymphokine function or production</td>
<td>Rats (224)</td>
</tr>
</tbody>
</table>

refrained with distemper virus, which is similar to human measles virus, had decreased survival time and increased incidence of encephalitis and mortality (230, 231). Another study in dogs showed increased morbidity and mortality from Salmonella in overfed animals (231).

CLINICAL AND PUBLIC HEALTH EXPERIENCE

It should be obvious from the evidence for the effects of individual infections on nutritional status that any factors that increase the burden of infection are of clinical and public health importance. Given the multiple effects of nutritional deficiencies on immune function, it is clear that these deficiencies increase the frequency and severity of infections in poorly nourished populations. In children the result is impaired growth and development and in adults time lost from work and decreased work productivity. The only rational public health response is a combination of measures that will reduce infection, including improved environmental and personal hygiene, immunizations, and a better diet to improve nutritional status and thereby reduce morbidity from infections.

Most nutrients are directly or indirectly involved in protein synthesis and most immune responses involve the production of proteins with specific functions. Because there are only a limited number of possible alterations of the immune system, it is not surprising that lists of the observed effects of individual nutrient deficiencies tend to be similar. T cell functions are more sensitive than B cell functions to most nutrient deficiencies. Thus, a few specific immune tests such as of phagocytic capacity, T cell subtypes, complement levels, and delayed cutaneous hypersensitivity can be useful indicators of malnutrition and indicate the need to identify and combat the specific nutritional deficiencies responsible. Iron deficiency and protein-energy malnutrition, both highly prevalent, have the greatest public health importance.

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