

Iron-Zinc, Immune Responses, and Infection

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Micronutrients, the immune system and resistance to infection form a veritable trinity. Each one influences the others. Although the influence of diet on risk of infectious disease has been known for centuries, it is only in the last 25 years that the importance of impaired immune responses as an intermediate risk factor has been documented (1,2). It is now established that malnutrition in its broadest definition alters the immune system; the most affected responses include cell-mediated immunity, phagocytes, complement system, mucosal immunity, and the amount and quality of selected antibody responses. The effects of iron and zinc on immunity have been studied extensively.

It is important to recognize the complexity and interdependence of immune responses and the sensitive and functional effects of nutritional intake and status on immunity and susceptibility to infection. This has been reviewed extensively (3–10) and is alluded to in other chapters in this book.

HOST DEFENSES

Host defense mechanisms have been described in depth elsewhere (11,12). For the nonspecialist reader, it may be appropriate to present a simple view of immunity as a protective umbrella (Fig. 1) and as a bridge of life (2) (Fig. 2). The immune responses can be broadly divided into two main tiers: nonspecific and antigen-specific. The nonspecific defenses include the skin and mucous membranes, phagocytic cells, mucus, cilia, complement, lysozyme, interferon, and other humoral factors. These innate processes are naturally present and are not influenced by previous contact with an infectious agent. They act as the first line of protection and retard the establishment of overt infection. Antigen-specific mechanisms include the B-cell system of antibody

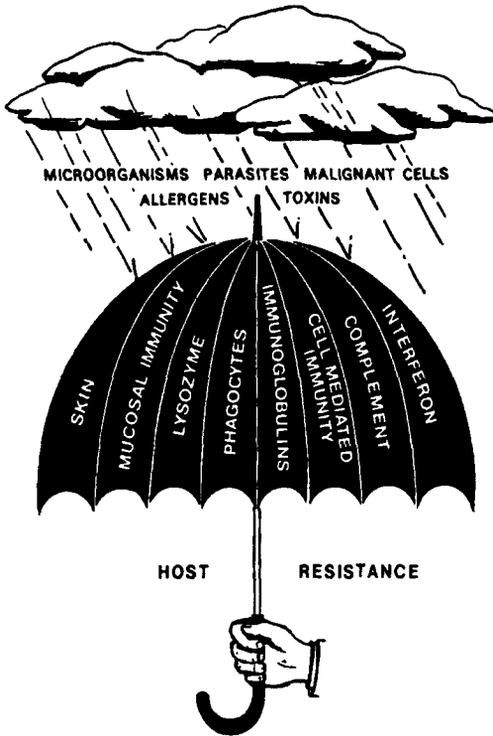


FIG. 1. A simple view of host defenses as a protective umbrella, consisting of physical barriers (skin and mucous membranes), nonspecific mechanisms (complement, interferon, lysozyme, and phagocytes), and antigen-specific processes (antibodies of five immunoglobulin isotypes and cell-mediated immunity). From Chandra RK and ARTS Biomedical Publishers (2); with permission.

production and the T-cell system of cell-mediated immunity. These mechanisms are adaptive and acquired in that they are specific reactions induced by previous exposure to a microorganism or its antigenic determinants. They are effective in checking the spread of infection and eradicating the invading organism. The specific immune responses form the basis of prophylactic immunization against common communicable diseases such as measles, respiratory illness caused by *Haemophilus influenzae*, and systemic disease caused by *Salmonella* organisms. In the body, nonspecific and antigen-specific defenses act in concert.

MICRONUTRIENTS AND IMMUNITY

A few general concepts of the interactions of trace elements, immune responses, and infectious disease should be highlighted (13). First, alterations in immune responses occur early in the course of a reduction in micronutrient intake (Fig. 3). Second, the extent of immunologic impairment depends on the type of nutrient involved, its interactions with other essential nutrients, the severity of deficiency, the presence of

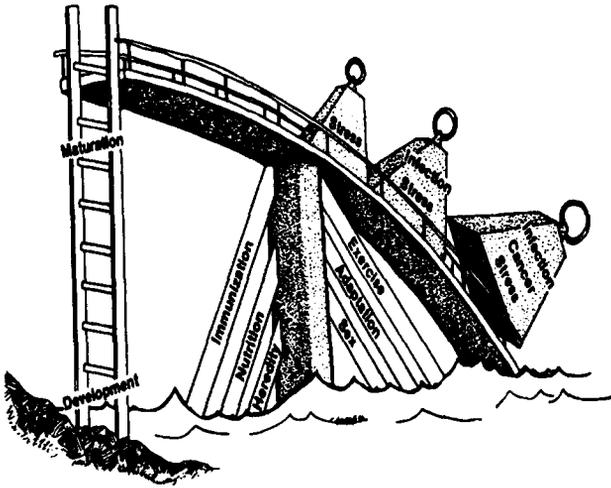


FIG. 2. The immune system is a bridge of life. During fetal and early postnatal life, it undergoes development and maturation. Heredity, sex, adaptation, exercise, immunization, and nutrition are important determinants. Stress, infection, and diseases such as cancer can further impair immunity and end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

concomitant infection, and the age of the subject. Third, immunologic abnormalities predict outcome, particularly the risk of infection and mortality. Fourth, for many micronutrients, excessive intake is associated with impaired immune response. Finally, tests of immunocompetence are useful in titration of physiologic needs and in assessment of safe lower and upper limits of micronutrient intake.

In this chapter, I will present a selective review of the impact of iron status and zinc status on immune responses and susceptibility to infection. The roles played by other

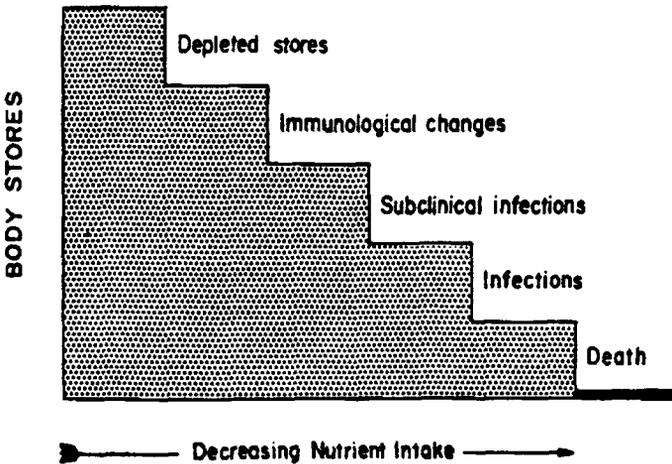


FIG. 3. Impact of decreasing intake of trace elements on immunity and infection.

trace elements (*e.g.*, selenium), vitamins, and fatty acids are discussed in other chapters.

IRON

Iron has been dubbed a *two-edged sword*. On the one hand, the element is required for the *in vitro* growth of most bacteria and fungi, with the exception of lactobacillus. If antibody is added to an iron chelating compound such as lactoferrin, the growth of bacteria such as *Escherichia coli* in the test tube is severely restricted (14). The effect of *excess* iron—that is in amounts that exceed those in normal culture media—has not been well characterized. The extrapolation of these *in vitro* conditions to the *in vivo* situation, particularly in humans, is moot.

Kochan (15) coined the term *iron nutritional immunity* to denote hypoferremia as a common feature of infectious disease and the inhibition of bacterial growth when culture medium is depleted of iron. But clinical data do not support any significant role of iron excess or deficiency as a determinant of the recurrence or severity of infectious disease in humans (16–18).

In this context, it should be emphasized that a similar reduction in serum zinc levels has been noted in infections. Does this imply that reduced zinc availability is a potent host defense? No one seems to suggest that, nor does any objective evidence point to it.

No controversy exists about the deleterious effects of iron deficiency on immune responses; almost all published studies indicate that individuals with iron deficiency show impairment of cell-mediated immunity (delayed cutaneous hypersensitivity responses, T-lymphocyte proliferation response to mitogens and antigens), phagocyte microbicidal function, and mucosal immunity. These findings have been documented in studies reported from many centers. These alterations may well be linked to changes in the activity of scores of iron-dependent enzymes such as myeloperoxidase and ribonucleotide reductase. In addition, physical changes in the mucosal epithelia may also be important. Recently, iron deficiency has been shown to reduce natural killer cell activity and the production of cytokines such as interleukin-2 and interferon- γ (14). A recent study indicates that the presence of iron helped monocytes to suppress the growth of *Mycobacterium tuberculosis* (19). Iron-mediated growth suppression was correlated with selective suppression of tumor necrosis factor- α (TNF- α) release from infected monocytes and iron decreased monocyte sensitivity to exogenously added TNF.

What is apparently controversial is the relation between iron status and risk of infection. This has been reviewed in several publications that purport to present a balanced view of the topic (16–18). The consensus may be stated simply: in humans, iron deficiency is associated with an increased risk of infections and its prevention or treatment may be expected to lower the incidence of common infections. In these circumstances, oral iron administration in conventional doses is safe and effective. In a few selected instances, it is prudent to delay or withhold iron therapy, particularly systemic parenteral therapy; these include very low birthweight infants, young chil-

dren with severe protein-energy malnutrition and reduced serum transferrin levels, patients with existing bacterial infection, and so on.

Chronic iron overload states such as hemochromatosis with high, almost complete, saturation of transferrin do not result in increased incidence and severity of infection; death is more often caused by cardiac and hepatic failure, hepatoma, and diabetes (20). Nearly 10% of patients do die of infection but then the role of underlying liver disease and diabetes cannot be discounted. In thalassemia, the effective control of iron load may result in serious infection, not when the iron load is at its peak.

Many of the clinical epidemiologic studies on this topic are handicapped by poor study design, inadequate analysis, and biased interpretation of results.

ZINC

The essentiality of zinc for mammals is well documented (17,21,22). In humans, the most dramatic example is the syndrome of acrodermatitis enteropathica in which infants are unable to absorb an adequate quantity of zinc, resulting in a low serum zinc level and the clinical manifestations of zinc deficiency with hair changes, poor growth, diarrhea, rash, and life-threatening infections. Low levels of serum zinc are linked to impaired cell-mediated immunity (23). Before we could diagnose and treat these patients with zinc supplements, they would die in infancy. Today, with appropriate treatment, they can lead an almost normal life. The relation of chronic low zinc intake and poor absorption with growth failure, rash, diarrhea, hypogonadism, and infection was observed in the Middle East. In hospital, in patients on total parenteral nutrition in the 1970s, we also observed many patients with acquired zinc deficiency.

Zinc-dependent enzymes number in the hundreds (21). Many of these are critical for cellular metabolic pathways, including those that mediate the functions of phagocytes and lymphocytes. Zinc regulates the function of superantigens (24). It is not surprising, then, that zinc deficiency results in profound immunodeficiency (25). The salient changes observed are in (a) phagocytes—nicotinamide adenine dinucleotide phosphate reduced ingestion of microorganisms, impaired chemotactic migration, decreased activity of reduced oxidase, which is a cofactor for phospholipases A2 and C, instability of cell membranes possibly owing to oxidation of arachidonic acid by iron complexes; (b) cell-mediated immunity—reduced lymphocyte proliferation response, decreased CD4:CD8 cell ratio and helper function, impaired natural killer cell function, reduced thymulin activity (Fig. 4); and (c) decreased antibody production after challenge with T-cell dependent antigens and alloantigens. The role of zinc in various metabolic and cellular functions is summarized in Figure 5. It should be made clear, however, that further studies are needed to confirm these initial data. A case in point is the importance of zinc in apoptosis.

Several field studies have confirmed the important role of zinc in immunity and risk of infection. For example, young children in underprivileged communities given a zinc supplement (10 mg) daily showed reduced susceptibility to both diarrhea and respiratory infection (26) (Chandra RK, unpublished data, 2000). Boys and the very

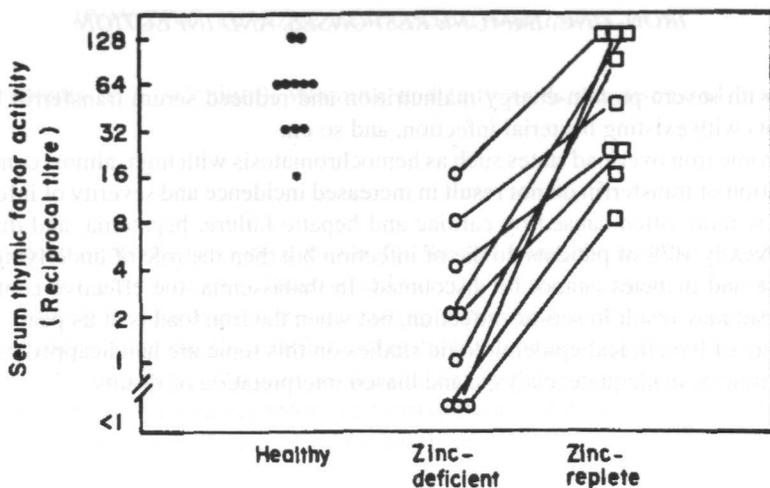


FIG. 4. Serum thymic factor activity in zinc deficiency and effect of zinc treatment.

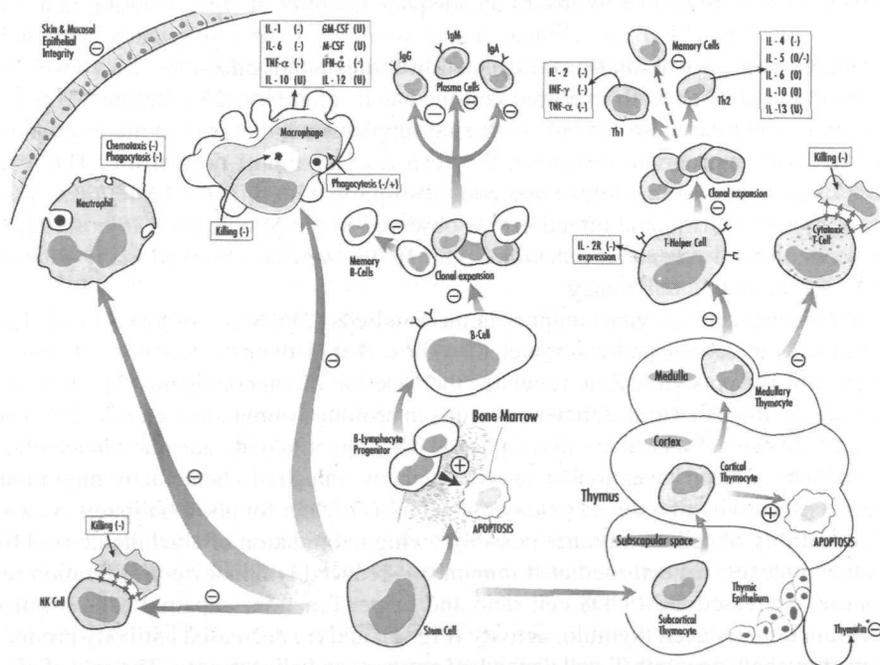


FIG. 5. The effects of zinc on the development and function of certain immunologic cells and cytokines. GM-CSF, granulocyte-macrophage colony-stimulating factor; IG, immunoglobulin; IFN, interferon; IL, interleukin; IL-2R, interleukin-2 receptor; M-CSF, monocyte colony-stimulating factor; NK, natural killer; O, zinc deficiency has little or no effect on the process or activity; TNF, tumor necrosis factor; U, the effect of zinc deficiency on the particular process or activity is unknown; -, zinc deficiency downregulates or inhibits the process or activity, +, zinc deficiency enhances the process or activity; *, zinc is needed for the structural integrity of the molecule. From the authors Shankar AH and Prasad AS, and the American Society for Clinical Nutrition (21); with permission.

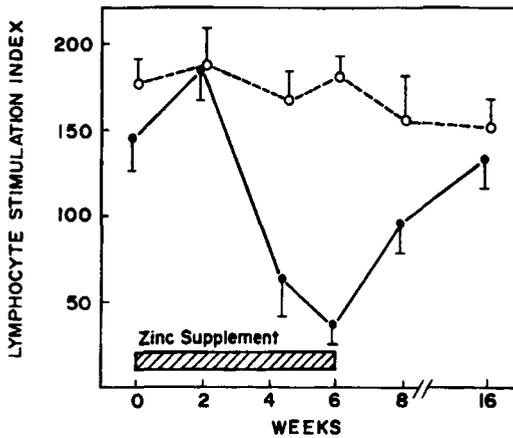


FIG. 6. Lymphocyte stimulation response in healthy adult men given 300 mg zinc supplement daily for 6 weeks (●) compared with results in nonsupplemented controls (○). From the Chandra RK, and the American Medical Association (28); with permission.

young, and those whose initial serum zinc level was low, benefited the most. Whether this benefit is the direct result of zinc or an indirect effect through better availability of other nutrients such as vitamin A needs further study.

In the elderly, zinc is an integral component of the highly effective micronutrient supplement that results in enhanced immunity and reduced incidence of infection (27).

Low birthweight infants show impaired immune responses and an increased incidence of infection. In both preterm and small-for-gestational age infants, zinc supplements (1 mg/kg body weight) enhance immune responses and reduce infection rates (Chandra RK, unpublished data, 2000; in preparation). This topic is reviewed extensively in another part of this book.

Whereas the essentiality of zinc for immunity has been established, it is also true that excessive intake of the element can decrease selected aspects of the immune repertoire (28) (Fig. 6); it may well be that this could enhance risk of infection and other disorders.

In addition, the important interactions between zinc and other trace elements and heavy metals is recognized. For example, zinc supplements abrogate the deleterious immunologic effects of cadmium (29–32).

CONCLUSIONS

Both iron and zinc are essential for the integrity and function of the immune system. For these trace elements, as for nutrition in general, the sane advice is “balance, variety, and moderation.”

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DISCUSSION

Dr. Zoppi: I have a question about iron deficiency and impairment of the immune response. We know that two physiologic conditions exist in the first year of life where the infant has an

iron-deficient anemia: physiologic anemia and anemia from cow's milk feeding. Do you think these two conditions can impair the immune response in children in developed countries?

Dr. Chandra: Little information is found on immune responses in the first 3 months of life, when the so-called *physiologic anemia* appears (1). Studies in preterm infants have shown that where there was a more exaggerated reduction in iron level with or without anemia at around 6 or 9 months of age, there was a reduction in immune response (2). Data on the prevalence or incidence of infection are difficult to interpret because of several confounding variables. Nevertheless, there is some suggestion that common infections may be increased in these infants.

Dr. Haschke: In the very low birthweight infant, the view of the US Food and Drug Administration seems to be that uncritical iron supplementation could be dangerous. Those infants with birthweights between 500 g and 1,500 g receive repeated blood transfusions, so they get a lot of iron from that source, and uncritical supplementation with iron-fortified formula is perhaps not the best way to get the iron into the body. One should leave it to the doctor who is treating the baby to decide when and how much iron should be given, in particular in situations where erythropoietin is used as treatment. Would you agree on that?

Dr. Chandra: Yes. With repeated blood transfusions that many very low birthweight babies receive during the first few weeks of life, no need is really seen for additional iron supplementation. Also, iron utilization in the first 3 or 4 months in these babies is very low. The question really is whether an iron-fortified formula should be given from birth so the mother does not have to change formulas around 4 and 6 months, when iron is really needed. It is like giving fluoride supplements in the first 6 months of life, even though they are not needed at that time—you want to condition the mother to start giving them on a regular basis. However, if the mother is intelligent and cooperative and the physician has a good relationship with her, then an iron-fortified formula can and should be started some time after 4 months.

Dr. Marini: Twenty years ago we did a study where we gave 12 mg/d of iron, about 2–3 mg/kg, to one group of low birthweight infants, and another group was given 1 mg/kg. When we looked at these babies at 6 months and 9 months, the babies receiving the higher amount of iron had higher ferritin concentrations and better cardiovascular function, independent of hemoglobin levels (3). This is another example of a nonhematologic effect of iron administration. I remember Oski's study showing that babies with low iron had some impairment of secretion of catecholamines (4). In relation to the risk of infection when giving iron to preterm babies, I think that most intensive care units now give iron because it is necessary to increase the iron intake when giving erythropoietin. Sometimes, in order to achieve an effect and to avoid the need for blood transfusion, we give up to 6 to 8 mg/kg/d of iron to these babies, for about a month. No evidence is seen at all of an increased risk of infection in these babies. So, I think iron is extremely important for preterm babies. The problem of iron toxicity is mainly related to the first week of life, when there may be an increase in free iron in very small preterm babies. This may result in superoxide or free radical damage.

I have a practical question about the clinical value of measuring blood levels of zinc in these babies. When you did your study on zinc supplementation, did you find that zincemia changed in parallel with thymic function, to show that we really need to give zinc to these babies? And is there a relation between zinc and iron, as with calcium and phosphate? Is there an interaction between the two?

Dr. Chandra: I agree with your comments on the nonhematologic effects of iron. So far as your questions are concerned, variations in serum zinc concentration reflect body zinc under conditions of very significant zinc deficiency. The blood pool of zinc is only a very small fraction of total body zinc. Thus, when giving zinc supplements to a zinc-deficient individual, you cannot expect serum zinc to change very dramatically in the short term, even though zinc-dependent functions may change. This is another example where functional changes in enzyme

activity and immune responses are more important than measuring levels of serum zinc, which is a notoriously poor indicator of marginal zinc deficiency. So far as the ratio of zinc and iron is concerned, 1:5 or 1:7 would be an optimal ratio that is safe for oral intake.

Dr. Haschke: What about older infants and toddlers, who tend to have a lot of infections and in whom the hemoglobin is on the low side and iron deficiency quite common? In industrialized countries, it has been shown that iron-fortified formulas are safe for infants. Would you say that the same can be said for developing countries? I am not talking about Chile, because in this respect Chile is no longer a developing country, and it has a very low infection rate.

Dr. Chandra: I know of no evidence that iron-fortified formulas would do any harm. Although Chile is different now from many other developing countries, at the time those studies were done, in the urban slums of Santiago (5), the conditions were not very different in terms of sanitation and recovery of fecal pathogenic microorganisms from those in many other developing countries. The consensus of evidence suggests that iron-fortified formulas would do no harm and perhaps could be of benefit to infants, even to toddlers. Of course, other considerations, apart from immunity and infection, are seen. There are the questions of physical activity, temperature regulation, developmental achievement, and many other aspects of body functions impaired by iron deficiency that could be improved by giving an iron-fortified cereal or formula or both. There is also growing concern that the type of iron used in formulas is important. Some types of iron supplement may be more likely to cause oxidative damage than others. Polymaltose, for example, has been shown *in vitro* to be safer than ferrous sulfate or ferrous gluconate. This is a question that has not been looked at adequately so far.

Dr. Coovadia: I have a comment and a question. The comment is in relation to an additional hazard of iron deficiency. This has to do with the rate of vertical transmission of HIV in developing countries. Many risk factors are seen for vertical transmission, but when we looked carefully at our population—they are all Africans and not in the late stages of HIV—we found that one of the more powerful risk factors was anemia in the mother. This raises the prospect of reversal by giving supplements.

My question is related to respiratory infections and micronutrients. On reviewing the literature, I was struck by the variety of definitions of respiratory infection. Some people include the common cold, others talk about *upper respiratory infections*. In the low birthweight baby, what sort of infections are these respiratory infections and how are they diagnosed?

Dr. Chandra: Mostly, these were upper respiratory infections, diagnosed by symptoms such as runny nose, cough lasting 48 or more hours, feeding problems, and pyrexia. In many infants, we had results of ancillary investigations (*e.g.*, total and differential white cell counts, chest radiograph, and C-reactive protein) to support the presence of bacterial infection.

In relation to your comment, I should mention that the type of micronutrient deficiency that is linked to higher or lower transmission rate of HIV from mother to infant seems to vary in different studies. This is a puzzle that I have not been able to solve satisfactorily. In some studies, high vitamin B₁₂ levels seem to correlate best with vertical transmission. In others, it is low B₆ level. The same applies to adult patients with HIV in whom nutrient intakes and blood levels correlate with disease progression or CD4 counts. Once again, deficiency of a variety of nutrients has been found to be linked with disease progression. Which of these is the most critical remains to be determined. Perhaps most of these may have some effect, depending on the setting.

Dr. Woodward: With reference to the comments you made about the bactericidal activity of neutrophils in iron deficiency, is there evidence of an influence in the absence of overt infection?

Dr. Chandra: Yes, there is. Even without obvious infection, phagocyte bactericidal capacity is compromised in iron deficiency, which correlates metabolic activity and levels of several of the iron-dependent enzymes (2). Infection causes further impairment of bacterial killing capacity.

Dr. Wasantwisut: I would be interested to hear your comments about malaria infection. Lavender has shown decreased parasite infestation in his selenium-deficient, vitamin E-deficient mice. *Plasmodium burkii* was used as the malaria model. This is in contrast to coxsackie virus, which shows increased virulence in this deficient model. It has also been shown that when malnourished refugees enter camps they have an increase in malaria incidence after they have been fed good food and rehabilitated for some time.

Dr. Chandra: You are right that in those studies by Levander et al., the effects were opposite to what his group later showed for coxsackie virus. The reasons are not clear. I do not think he had an explanation either. The discrepancy might reflect the species of malaria: one species may not be affected by iron status, whereas another might be. Also, in the clinical situation, one must distinguish between the prevalence of parasitemia and the occurrence of symptoms; the two may not go in the same direction. Evidence seems to indicate that symptoms can be exacerbated, whereas parasitemia may not change.

Dr. Keusch: Malaria occupies a very special niche in the host with respect to iron, because it lives in the red cell. In fact, it lives on hemoglobin. It eats the globin portion, uses the amino acids, and spits out the iron. So, there is clearly going to be a very special relationship between malaria and states of iron deficiency or sufficiency. In the context of Dr. Chandra's comment about the species of malaria perhaps being important, it is relevant that iron given to an iron-deficient subject enhances erythropoiesis, and *P. vivax* preferentially lives in young erythrocytes. So, it would be surprising if there was not an increase in the numbers of red cells parasitized and the total number of parasites present in the blood. What is striking is that in very well conducted studies in Papua New Guinea, no effect was seen of iron supplementation in iron-deficient subjects on clinical malaria, as Dr. Chandra pointed out. The only way to interpret that finding, in the face of enhanced parasitemia, is that the iron is also supplementing the immune response and allowing the host to control the enhanced growth of malaria. So it is a very special situation, and the clinical evidence is certainly that iron supplementation in that circumstance does no harm. I think we are ready to close the book on the iron nutrition or immunity hypothesis with respect to dealing with iron deficiency at a population level, and one thing we can do in this conference is to make a very strong statement in that regard.

Secondly, in the context of iron therapy in more acute situations, in protein-energy malnutrition, for example, I do think one has to be careful of loading iron into subjects who are not synthesizing iron transport proteins; under those circumstances, increases in free iron are likely to enhance microbial growth. It is a very special circumstance, but the recommendations are not to use iron in the initial repletion and to wait a week or two. At the point at which transferrin is increasing, it is completely safe to give iron. So, I think it is time to close the chapter on that book.

Dr. Chandra: I wholeheartedly agree. I should also say that once a child with protein-energy malnutrition is put on an appropriate diet, it does not take long—just the matter of a week or 10 days—before transferrin levels begin to rise, so the period during which iron therapy should be withheld is very short [1].

Dr. Coovadia: I was intrigued by your caution over where we should not use iron: severe protein-energy malnutrition, low birthweight babies, and latent infections. How do I translate the last one into practice, and what does it mean?

Dr. Chandra: By that, I mean patients who are, for example, in intensive care units, partic-

ularly those with multiple trauma. Some of these may be harboring infections. Even if it is useful to give other forms of nutritional supplementation, including most of the micronutrients, iron should not be given in the first week or 10 days.

Dr. Suskind: Just one comment with regard to the use of iron in protein-energy malnutrition. In several studies that we did in Thailand in the 1970s, we did in fact use iron from the time of admission in children who were severely malnourished, provided that they were on antibiotic coverage for infection. We found that we did not have any problems with aggressively treating the malnourished child with both antibiotics and iron simultaneously. Initially, we used Imferon but then switched to an oral preparation.

Dr. Chandra: There could be a greater concern about the use of iron-dextran, perhaps because of the effect of dextran rather than the iron. Large amounts of dextran may compromise reticuloendothelial function temporarily.

Dr. Klish: One of the issues that is smoldering around iron supplementation in the United States has to do with supplementation of the breast-fed infant, the argument being that iron supplementation saturates lactoferrin, which alters the intestinal milieu, which alters the bacterial mix in the intestinal tract. I am not sure there are any data to support that contention, but do you have any comments about it?

Dr. Chandra: In fact, data are found to the contrary, that iron supplements do not alter microflora (6). So far as the timing of giving iron to breast-fed babies is concerned, supplements are indicated if formula intake is more than 30% of total energy intake. So long as energy intake from formula is less than 30% of the total, supplementary iron is not needed in breast-fed infants up to 6 months of age.

Dr. Valyasevi: In Thailand, there is a high incidence of iron deficiency anemia and at the same time we have a high prevalence of thalassemia. My question is, what are the hazards of iron overload if iron is given as a public health measure in such a population?

Dr. Chandra: Thalassemia is a very special situation where even more caution with respect of iron supplements needs to be exercised, especially for thalassemia major. I do not think it would be a problem with thalassemia minor, where the iron load is minimal at best. I do not know about the prevalence of thalassemia major in Thailand. In certain parts of India, it is of the order of three per 1,000. So you are looking at a very small population and by the time the infants are even 1 year of age, the clinical diagnosis is obvious. A clinician who makes this diagnosis should be cautious about iron intake in such a child, I do not think it should affect national pediatric policy of giving prophylactic iron to prevent iron deficiency. The amount of iron overload is minimal and it takes 10 to 15 years before it becomes significant. Moreover, in the patients of thalassemia who die in the second decade of life or later, the cause of death is liver failure, heart failure, and diabetes, rather than infection.

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