Host-Pathogen Interactions: Can Micronutrients Tip the Balance?1–3

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Abstract

Nutrients are essential to the human host and to its invading pathogens. The purpose of this International Nutrition Council symposium on Micronutrient Regulation of Host-Pathogen Interactions held at Experimental Biology 2006 was to examine new knowledge about the mechanisms by which certain limiting micronutrients can mediate the balance of power between the human host and its numerous potential pathogens. In this introductory article, we briefly review how competition for nutrients is critical to the survival of both host and pathogen and describe some of the evolved mechanisms by which each attempts to gain supremacy over the other. We provide examples of how the presence or absence of certain mechanisms for nutrient acquisition can govern the niche specificity of organisms. We then describe some of the extensive evidence suggesting that, of all the nutrients, iron plays an especially crucial role in host-pathogen interactions.

To this end, we provide a reminder of early studies suggesting that universal iron administration under conditions of high pathogen exposure may lead to adverse consequences. Finally, we provide some cautionary tales in the form of intervention studies in which the administration of other micronutrients yielded unpredicted adverse effects. These lessons emphasize the need to step back from an unbalanced concentration of research funds on empirical trials (often built on an inadequate theoretical basis) and toward a greater concentration on integrated clinical research into nutrient effects on host defenses and pathogen virulence.


From the earliest days of evolution, higher organisms have provided lower organisms (bacteria, viruses, and protozoa) with an attractive ecological niche in which they have a ready supply of nutrients, warmth, protection, and convenient routes of transmission. Some of these lower organisms are benign, even beneficial, symbionts, whereas others are deadly pathogens. Between these 2 extremes lies a wide spectrum of infectious agents whose infectivity and pathogenicity (and hence, clinical outcome) are modulated by a variety of host factors, especially the innate and adaptive immune systems. In an evolutionary sense, this constant battle between host and pathogen has, by definition, been very finely balanced; if this were not the case, either the host or the pathogen in question would be extinct.

In addition to the immune responses, a host’s ability to deprive microorganisms of nutrients is another mechanism by which it can attempt to maintain ascendancy over possible pathogens. This may be particularly critical for certain potentially limiting micronutrients. Iron is a good example in which there is abundant evidence, summarized below and in the accompanying article by Doherty (1) in this issue, that it plays a particularly critical role in host-pathogen conflict. Subtle alterations in iron supply may tip the balance of power toward the pathogen and can rapidly lead to aggressive disease and death. A similar principle may be true for other trace elements.

Micronutrients are also critical to the optimal functioning of the host’s immune response. For example, as described in the article by Beck (2), deficiency in micronutrients involved in the maintenance of host oxidant defense (e.g., selenium and vitamin E) has been shown to induce changes in viral genomes that can transform benign variants into pathogens. Other micronutrients such as zinc and vitamin A play a particularly important role in maintaining host cellular integrity and efficient component functioning of the adaptive defenses.

This is a highly active field in which new technologies (especially in relation to both host and pathogen gene analysis)
and recent advances in describing the molecular mechanisms of nutrient handling and competition (e.g. the cloning and subsequent study of nutrient transporters) are opening up new lines of understanding and research. This symposium considers the implications of these new findings for human health, with papers focusing on selenium/vitamin E, iron, and zinc. This paper sets the scene by highlighting some of the basic issues relevant to the host-pathogen battle for nutrients.

**Regulation of nutrient availability to pathogens: the acute phase response of the host**

The acute phase response represents a coordinated series of cytokine-driven host adaptations designed to combat acute crises and infections. Prominent among these adaptations are homeostatic alterations in nutrient partitioning whose main purpose seems to be to deprive the systemic circulation of micronutrients that would be required for successful pathogen growth (4). Figure 1 illustrates approximate changes reported from the literature. Most, but not all, of these alterations are mediated by changes in the levels of binding proteins, such as ferritin (a positive acute phase protein designed to sequester iron) and retinol-binding protein (a negative acute phase protein whose levels are suppressed to reduce mobilization from the liver). Host tissues can withstand a temporary withdrawal of micronutrient supply better than the pathogens this temporary handicap carries an overall survival benefit.

If we are correct in interpreting this adaptive suppression of host micronutrient status (at least in the systemic circulation) as a survival trait honed by millions of generations, we should perhaps be more circumspect in our desire to override the response by the medical provision of extra micronutrients (see below for further discussion of this point in relation to iron).

**Nutrient regulation of niche specificity of microorganisms**

The general principle of sensitivity of organisms to the nutrient composition of the host milieu can be illustrated by 2 examples of niche specificity. The first is the so-called organotropism of *Chlamydia trachomatis*. Caldwell et al. (5) applied functional genomics to demonstrate that all ocular trachoma isolates tested have inactivating mutations in the tryptophan synthase gene (trpBA), whereas all genital isolates encode a functional enzyme, and this functionality is directly correlated to IFN-γ-mediated eradication and thus establish persistent infection.

A second example involves the ability of only certain strains of *Escherichia coli* to colonize the low-iron environment of the urinary tract. Under normal circumstances, the human urinary tract is able to resist microbial infection. To cause urinary tract infection, an organism has to evade host defense mechanisms by possessing distinct properties that contribute to its virulence; genes encoding these are concentrated in highly variable regions of the genome frequently termed high pathogenicity islands. Virulence determinants of uropathogenic *E. coli* include adhesins, polysaccharide coating, hemolysin production, and outer membrane proteins, but prominent among these (and amid the pathogenicity islands for numerous other bacteria) are genes encoding for iron-binding siderophores (6), thus illustrating the importance of the competition for iron in determining who wins the host-pathogen battle.

**Is iron an especially critical micronutrient?**

As noted above, numerous micronutrients play a special role in human immune function, but a case can be made that iron is preeminent in its position at the center of the host-pathogen battle. The accompanying paper in this series by Doherty (1) considers the role of iron in more detail, so here we confine ourselves to some historical and more theoretical considerations as to why iron is so crucial.

As far back as 1944 Schade and Caroline (7) published a seminal paper in Science illustrating that a component of raw hen egg white inhibited the growth of several species of bacteria and that this inhibition could be overcome by adding more iron. In 1946 they published a second Science paper describing for the first time “an iron bonding component of human blood plasma” (8). These papers started decades of experiments (Figs. 2 and 3) that demonstrated the interplay between iron and iron-binding proteins in modulating bacterial growth. We now know that most pathogenic microorganisms evolved sophisticated methods

![FIGURE 1](image)

**FIGURE 1** Effects of the acute phase response on plasma micronutrients. Approximate changes gathered from a variety of sources.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Approximate Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free iron</td>
<td>~50%</td>
</tr>
<tr>
<td>Zinc</td>
<td>~50%</td>
</tr>
<tr>
<td>Selenium</td>
<td>~50%</td>
</tr>
<tr>
<td>Retinol</td>
<td>~50%</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>~60%</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>~50%</td>
</tr>
<tr>
<td>Ascorbate</td>
<td>~70%</td>
</tr>
<tr>
<td>Copper</td>
<td>~30%</td>
</tr>
</tbody>
</table>

![FIGURE 2](image)

**FIGURE 2** In vitro viability of *S. mutans* with apolactoferrin ± iron. Reproduced with permission from Arnold et al. (9). CFU, colony forming units; Fe Sat LF, iron-saturated lactoferrin; apo LF, iron-free apo-lactoferrin.
for acquiring iron in an iron-deplete environment by producing specific iron chelators (siderophores), of which there are over 500 known variants (11). Genetic detective work shows that these iron-acquisition mechanisms occupy a disproportionate fraction of the bacterial genome, emphasizing their importance. One particular example of such work provides an elegant indication of the centrality of iron. In 2001 Parkhill et al. (12) published the full genome sequence of *Yersinia pestis*, the causative organism for plague. A small percentage of the genome underwent degradative evolution (i.e. it carries the fingerprint of recognizable genes that are no longer able to be expressed). These genes indicate that the organism used to occupy an enteric niche (e.g. they express genes for flagellae). A further small percentage of the genome shows evidence of recent horizontal capture from other bacteria. It is assumed that these new genes enabled *Y. pestis* to make the transition from being an enteric to a systemic organism, and prominent among these are genes for iron sequestration, thus again emphasizing the individuality of iron.

In response to these iron-acquiring strategies that have evolved in microorganisms, the human host has evolved its own intricate strategies for transporting and storing iron in a bound state (transferrin, lactoferrin, ferritin, haptoglobin, and hemopexin) and, hence, depriving invading microorganisms of iron. These processes are more intricate for the regulation of iron than for any other micronutrients with the possible exception of zinc, as described by Prasad (3) in this volume.

**Lessons for nutritional interventions and some cautionary tales**

The chief lesson from these reminders of the competition between host and pathogen for nutrients is that the imprudent administration of additional micronutrients through supplementation programs aimed either at disease prevention or therapy may not always have a positive outcome. As early as the 1850s the Parisian physician Dr. Armand Trousseau warned his students of the mortal consequences of administering iron to tuberculosis patients (13) and there are many other similar cautionary tales regarding iron (14). The latest example, the halting by the data safety monitoring board of an extensive iron supplementation trial on Pemba Island due to an increase in the number of serious adverse outcomes in patients receiving iron (15), produced a wake-up call surprising to many. However, other researchers have not been surprised and would point out that the result is perhaps consistent with 60 y of basic science that has been too quickly forgotten. A summary of a WHO workshop analyzing the Pemba trial in relation to the background science on iron will be published in 2007.

Such lessons are not necessarily confined to iron. Large-scale intervention studies with various vitamins (e.g. vitamin E and β-carotene) have occasionally yielded adverse results with increased mortality or serious events in the supplemented patients. The issues are complex and conflicts between positive, neutral, or negative outcomes may ultimately be explained by differences in a population’s ecological setting (e.g. the adverse effect in Pemba compared with a neutral effect in Nepal may be due the presence of holoendemic malaria in Pemba), lifestyle behaviors (e.g. differential effects in smokers vs. nonsmokers), and their genetic profiles. Vitamin A provides a good example of how supplementation may have quite different effects in different age groups or against different disease backgrounds. Universal vitamin A supplementation for children in areas of marginal or severe vitamin A deficiency has been conclusively shown to save lives (16). However, recent reports suggest that vitamin A increases the risk of HIV-1 transmission through breastfeeding (17), may hasten (through postpartum maternal and neonatal supplementation) progression to death in breast-fed children who are HIV PCR negative at 6 wk (18), and increases diarrheal diseases and respiratory infections in peri-urban Mexican children (19). In a recent high-dose (International Vitamin A Consultative Group 2002 regime) vs. low-dose (current WHO regime) vitamin A supplementation trial, we found some evidence for possible adverse events in the high-dose patients (20), and this supports other reports that a lower dose of vitamin A may be more beneficial (21). Fawzi (22) has written a thoughtful critique on these studies that have produced greater harm than benefit. He suggests various possible explanations but is unable to progress beyond speculation because of the paucity of fundamental data as to how vitamin A modulates host immunity and what possible effects it might have in encouraging pathogen virulence.

**Conclusions and a suggested way forward**

This brief review reminds us that the interactions between, for example, a young African child and the pathogenic environment that may at any moment overwhelm his or her defenses are highly complex. Perhaps too many nutritional interventions have sought to short-cut the knowledge-gathering process and resorted to empirical trials in the hope of showing benefit. Some of these have been very successful, but, as indicated above, many instances of negative effects exist. Even in the cases where a positive effect seems conclusive (e.g. vitamin A and mortality, or zinc and diarrhea), we have little understanding of the mechanisms of action and hence are unable to refine the dose levels, mode of administration, target groups, or other variables that might yield even greater benefit. We propose that a more integrated approach to research (outlined in the lower section, Fig. 4) will ultimately save more lives than the current disparate approaches (top section of Fig. 4) and heavy emphasis on empirical trials that are often based on minimal background information in support of the hypothesized benefit. This argument needs careful articulation to the lobbies that subscribe to the
views: “something must be done” or “we have the knowledge, all that is required is to apply it.” Such sentiments are admirable, but, sadly, life is not so simple. Repairing and optimizing the performance of a complex machine, whether a living organism or a modern jet, will best be achieved with the aid of a detailed manual as to how it is constructed and how it is intended to operate. We are still very far from having a complete manual on the actions of micronutrients in human beings, so a high priority for such fundamental research remains.

**Literature Cited**