

## Iron and Immunocompetence

by R. K. Chandra, M.D.

Host-parasite interaction may be of no consequence or may result in colonization, subclinical infection, symptomatic disease or death. The factors that determine who among us are chosen to follow one path rather than the other remain poorly defined. Obviously the determinants of infection are not the determinants of symptomatic disease. In recent years, our knowledge of the range and mechanisms of immunity function and the factors modulating them has expanded remarkably. Does iron status have an effect on immunocompetence and thereby on susceptibility to infection? The answer is not clear. Vulnerability to infection based on the individual's state of iron nutrition must be the net result of the effect of iron or the lack of it, on microbial growth on the one hand and the host immune response on the other.

### Causes and Magnitude of the Problem

Iron deficiency is a worldwide nutritional problem.<sup>1</sup> The minimum estimates of prevalence range from 20 percent in industrialized countries to 60 percent in developing nations. The population groups particularly at risk of acquiring iron deficits are preschool children,<sup>2</sup> pregnant women,<sup>3</sup> old individuals and adolescents. Iron deficiency during pregnancy reduces tissue iron stores of the infant, a deficit which will persist if subsequent iron intake remains marginal.

The causes of iron undernutrition are varied. In socioeconomically poor groups, a low intake

of iron, frequent infections, parasitic infestation and a high incidence of low birth weight with consequent reduction in iron stores gained from the mother, are significant factors. Surprisingly, optimal iron nutrition is not invariable even in economically well-off individuals.<sup>4</sup> In them, the etiologic factors include reduced total intake of food, increased consumption of highly refined foods, use of aluminum and steel vessels rather than iron cookware, and a low degree of bioavailability of iron in certain food items. Occasionally, chronic occult blood loss may be a significant causal factor.

### Iron, Epithelial Structure and Cellular Enzymes

A variety of tissue changes associated with iron deficiency<sup>5</sup> may be attributable to deranged intracellular iron metabolism. Iron status is reported to be critical for the normal development and integrity of lymphoid tissues,<sup>6</sup> which control and modulate immunity. Epithelial changes have been described in iron-deficient individuals. Some of these alterations, e.g. koilonychia, are pathognomonic of iron deficiency, not being found in any other condition. Other lesions associated with iron deficiency include gastric atrophy, keratinization of buccal mucosa, bald smooth tongue, stunting of jejunal villi and the Paterson-Kelly syndrome of postcricoid obstruction and dysphagia. The last named is a premalignant lesion manifesting as dysphagia which is relieved symptomatically by iron therapy. It has been suggested that epithelial changes resulting from iron deficiency predispose to local infections, particularly by candida.<sup>7</sup>

A number of tissue enzymes contain iron or are influenced by iron-containing co-factors. These include cytochrome C, catalase, cytochrome oxidase, cytochrome C reductase, succinic dehydrogenase, aconitase, formi-

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minotransferase, peroxidase, tryptophan pyrrolase and xanthine oxidase. It is not unexpected, therefore, that iron depletion in man and in experimental animals is associated with a reduction in enzyme activity. Organs with a rapid cell turnover become rapidly depleted of iron-dependent enzymes. Enzymes with a slow turnover may remain relatively unaltered. One possible enzymic mechanism of reduced immunocompetence associated with iron deficiency is a change in the activity of myeloperoxidase contained in monocytes and polymorphonuclear leukocytes, the cells which phagocytose and inactivate bacteria.

### **Infection Frequency in Iron-Deficient Human Populations**

There is widespread belief that iron deficiency predisposes to infection. Infection, recurrent or severe, is the most common symptom for which iron-deficient children seek medical advice.<sup>9</sup> Several clinical surveys attempted to correlate iron status with the risk of infection. An Expert Group of the World Health Organization reported that individuals with nutritional anemia tend to have more frequent infection.<sup>1</sup> Mackay<sup>10</sup> observed a modest decrease in the number of episodes of bronchitis and gastroenteritis in iron-supplemented infants from low-income families in London. More recently, Andelman and Sered<sup>11</sup> found that respiratory infections were significantly less in infants who were given an iron-fortified milk formula. Iron-deficiency and impaired cellular immunity are common findings in patients with chronic mucocutaneous candidiasis.<sup>12</sup> The skin lesions as well as immunologic abnormalities reversed rapidly on administration of iron. Other studies failed to show a relationship between iron deficiency and infection frequency.<sup>13</sup> A recent study<sup>14</sup> of older children and adults with nutritional anemia found that iron-deficient individuals had a lower frequency of infection than did patients with other types of severe anemia, but there was no evaluation of any control group of healthy subjects. A high incidence of infection was seen in hyperferremic patients with hemolytic anemia. Chronic iron load associated with hemochromatosis, however, is not characterized by frequent infections.<sup>15</sup>

### **Iron Requirement for Microbial Growth**

Iron concentration and saturation of iron-binding proteins are major factors affecting the growth of microorganisms.<sup>16-18</sup> The assimilation of iron is a necessary prerequisite for bacterial and fungal growth. In order to extract free iron from tightly bound protein-iron complexes in mammalian tissues, bacteria produce siderophores with powerful iron-chelating properties, e.g. desferrioxamine, 2,3-dihydroxybenzoylserine, phenolates and hydroxamates, which bind, solubilize and assimilate the metal. The synthesis of siderophores is modulated largely by the concentration of iron in the immediate environment. The growth of most bacterial and fungal species is enhanced by the addition of iron to the culture medium and inhibited by serum having high unsaturated iron-binding capacity.<sup>19,20</sup> Bullen's<sup>21</sup> data on the inhibition of bacterial growth by lactoferrin and transferrin have a clinical application in the resistance of breast-fed babies, which is at least in part due to the high concentration of lactoferrin in human milk. Blood in body fluids may enhance bacterial and fungal infections and hasten death. If iron is added to plasma, microbial growth is inhibited until the transferrin becomes saturated with the metal. The hyperferremic serum of thalassemia patients promotes fungal growth which is inhibited by the addition of serum having a high unsaturated iron-binding capacity.<sup>22</sup>

### **Iron Status and Resistance to Infection in Animals**

The immunologic consequences of dietary iron deficiency have been evaluated in several animal models. Osborne and Davis<sup>23</sup> studied the effect of *Escherichia coli* endotoxin on young swine rendered iron deficient. Mortality was extremely high in the experimental anemic group. Antibody production in response to tetanus toxoid immunization was significantly reduced in rats that received inadequate dietary iron.<sup>24</sup> Baggs and Millor<sup>25</sup> studied the response to infection with *Salmonella typhimurium* in rats fed various levels of dietary iron. The susceptibility to infective challenge, assessed by morbidity and mortality, was enhanced in iron-deficient animals. Prewearing iron deprivation impaired the rats' ability to resist the

stress of infection, even if a period of nutritional rehabilitation had intervened. Inability to produce and deliver myeloperoxidase-containing cells was considered to be the pathogenesis of such vulnerability. Chu et al.<sup>25</sup> challenged iron-deficient and control rats with *Streptococcus pneumoniae* and observed a 1000-fold increase in susceptibility to infection in the deprived group.

There is some evidence, on the other hand, that the parenteral administration of iron compounds reduces the number of bacteria necessary to produce disease or death, whereas iron-chelating agents confer protection. Jackson and Burrows<sup>27</sup> observed that the growth of nonpigmented mutants of *Pasteurella pestis* was enhanced by injections of iron. In an experimental mouse model, Elin and Wolff<sup>28</sup> showed that changes in iron status secondary to administration of endotoxin or iron mediated the susceptibility of animals to challenge with *Candida albicans*.

#### Iron Deficiency and Immune Response in Man

Attempts have recently been made to study the capacity of iron-deficient subjects to mount immune response. Joynson et al.<sup>29</sup> studied cell-mediated immunity in adults with iron deficiency. Delayed hypersensitivity and lymphocyte transformation in response to purified protein derivative (PPD) of *Mycobacterium tuberculosis* and candida antigen were impaired in anemic compared with healthy groups. In addition, the production of macrophage migration inhibition factor was reduced when lymphocytes were stimulated with candida but not when PPD was employed. These observations, which were not repeated after iron therapy, could indicate reduced cellular immunity or lack of prior exposure to the antigen being used. Macdougall et al.<sup>30</sup> evaluated cellular defense mechanisms in children with latent iron deficiency, iron-deficiency anemia and healthy controls. Cutaneous delayed hypersensitivity in vivo and DNA synthesis in vitro by lymphocytes stimulated with phytohemagglutinin (PHA) and candida were impaired not only in anemic children but also in those having latent iron deficiency. Similar observations were made by Chandra and Saraya<sup>31</sup> who found, in addition, that the proportion of rosette-

forming thymus-dependent (T) lymphocytes which mediate cellular immunity, was slightly reduced in the iron-deficient group. The immunologic abnormalities were corrected on oral or parenteral administration of iron. Bhaskaram and Reddy<sup>32</sup> also reported a reversible reduction in the blastogenic ability of lymphocytes and in T-cells of iron-deficient children. Fletcher et al.<sup>12</sup> found lymphopenia and depressed lymphocyte transformation response in iron-deficient subjects, which returned to normal after correction of their iron status.

Gross et al.<sup>33</sup> found no statistically significant difference between cell-mediated immune responses of five iron-deficient subjects and controls but the two patients retested after administration of iron showed an improvement in lymphocyte activity in vitro. As opposed to these data, Kulapongs et al.<sup>34</sup> found normal lymphocyte response to PHA stimulation in eight children having iron-deficiency anemia and hookworm infestation.

An important first-line defense mechanism is the phagocyte system. In iron deficiency, opsonization and ingestion of bacteria by leukocytes was reported to be normal but intracellular digestion was reduced,<sup>35,36</sup> together with a lower metabolic response on phagocytosis. It was suggested<sup>35</sup> that iron deficiency might impair the activity of iron-dependent enzymes, such as myeloperoxidase, which contribute to bactericidal capacity of phagocytes.<sup>37</sup> Administration of iron was associated with a return of polymorph function within one week of starting therapy and prior to an increase in hemoglobin concentration, which suggests that tissue iron depletion rather than anemia is the critical factor influencing polymorph function.<sup>35</sup> Macdougall et al.<sup>30</sup> confirmed that bacterial killing by neutrophils of iron-deficient children was significantly less than that by control cells. Contrarily, one study on phagocytosis killing function of polymorphs in eight children with severe iron-deficiency anemia reported results within the range for healthy controls.<sup>34</sup>

#### Conclusion

Epidemiologic and clinical observations on the frequency of infections in iron-deficient human populations differ widely. The same is

true of disease states characterized by chronic iron overload. There is convincing evidence that the concentration of free iron is critical for microbial growth. The frequent association of reversible immunologic abnormalities in iron-deficient subjects has been observed in several studies and denied in others. The specific pathogenetic determinants and the role of concomitant infection in the causation of such immunologic defects, if present, remains unclear. It is likely that the outcome of an infective challenge in an iron-deficient organism will depend upon the balance of the effect of iron status on microbial multiplication and on host defense mechanisms. □

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