Functional Implications of Iron Deficiency

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Iron undernutrition is the most common single nutrient deficiency worldwide. Iron deficiency has often been presumed to have few deleterious effects unless severe enough to compromise cardiovascular function. Whereas the effect of reduced iron availability on hemoglobin levels and other hematopoietic indices has been well recognized for a long time, it is only recently that the association between iron deficiency itself, with or without anemia, on immunocompetence, cognition, physical work capacity, and other functions has been documented (1,2). A number of organs and systems show variable changes in structure and function, often before any drop in hemoglobin occurs. This is not surprising because iron is an integral component or an essential cofactor of several enzymes that play an important role in metabolic processes and cell proliferation; these include aconitase, catalase, cytochrome C, cytochrome C reductase, cytochrome oxidase, formiminotransferase, monoamine oxidase, myeloperoxidase, peroxidase, ribonucleotidyl reductase, succinic dehydrogenase, tyrosine hydroxylase, tryptophan pyrrolase, and xanthine oxidase (3,4). These enzymes are involved in a number of key pathways such as DNA synthesis, mitochondrial electron transport, catecholamine metabolism, neurotransmitter levels, detoxification, and other functions. Many iron-containing proteins, e.g., myoglobin, serve important functions. It is not surprising then, that iron deficiency results in a variety of functional abnormalities.

In this selective review, the effects of iron deficiency on immune responses and susceptibility to infection, muscle function and physical work capacity, cognitive function and behavior, gastrointestinal structure and function, and thermogenesis are briefly described.

IMMUNOCOMPETENCE AND INFECTION

On the one hand, free iron is essential for the multiplication of all bacteria, with the exception of Lactobacillus. In vitro studies showed that iron depletion of medium inhibits bacterial growth and iron excess promotes it (5), but the extent of in vivo saturation does not affect bacterial growth rate (6). On the other hand, iron is essential for the normal development and functional integrity of lymphoid tissues; iron deficiency may be expected to impair immune response mediated by lymphocytes and granulocytes (7,8).
Immune Responses

Iron deficiency results in a mild but detectable reduction in cell-mediated immunity. The proportion and absolute number of rosette-forming T cells is slightly decreased (Fig. 1), but normal figures may be seen. More consistent is a reduction in lymphocyte proliferation response to mitogens—phytohemagglutinin (PHA), Concanavalin A—and antigens (8-12) (Fig. 2). Impaired response is seen also in individuals with "latent" iron deficiency without anemia. The discrepant observations reported in one study of 8 patients with anemia from chronic blood loss due

![Image of Figure 1](image1.png)

**FIG. 1.** Proportion of rosette-forming T cells in iron-deficient children and iron-replete controls.

![Image of Figure 2](image2.png)

**FIG. 2.** Lymphocyte stimulation response to phytohemagglutinin in relation to transferrin saturation. In some patients, the test was repeated after 4 weeks of oral iron therapy. (From Chandra, ref. 37.)
to hookworm disease (13) may reflect differences in the cause of iron deficiency and in laboratory techniques. In another report (14), only 5 patients were investigated and iron deficiency was marginal (mean iron 54 μg/dl, range up to 88 μg/dl); the two subjects restudied after iron therapy showed a 44 to 55% increase in lymphocyte response to PHA. Hershko et al. (15) showed that, in chronic iron deficiency, the incorporation of radiolabeled thymidine into DNA was reduced together with decreased content of cellular DNA and impaired utilization of iron and glycine for heme and protein synthesis. The production of lymphokines, e.g., macrophage migration inhibition factor (MIF), in response to previously experienced antigens is reduced (9). Iron-deficient individuals may respond less often to recall antigens, e.g., candida, trichophyton, streptokinase-streptodornase, mumps, purified protein derivative (PPD); however, it must be emphasized that it is rare to encounter complete anergy in this group, unlike patients with protein-energy malnutrition.

Opsonization, ingestion, and chemotaxis are generally normal in iron deficiency in humans but intracellular bacterial and fungal killing is often reduced (16) (Fig. 3). It is important to employ an appropriate phagocyte:bacteria ratio, perhaps 1:5, and to construct kinetic curves of bacterial killing. In chronically iron-deficient rabbits, impaired uptake of opsonized *Staphylococcus aureus* by neutrophils was observed; the rate of phagocytosis could not be increased by autologous leukophilic α-globulin (17). Impaired reduction of nitroblue tetrazolium was observed when a quantitative test was conducted (16) but the result of the qualitative test in which the number of neutrophils with the reduced dye are counted was reported to be within the normal range (11,18). These apparently conflicting data are not incompatible since it is quite possible that the amount of dye reduced by each cell was

![FIG. 3. Microbicidal capacity of neutrophils in iron deficiency and controls. *S. aureus* was used as the test organism at a ratio of five bacteria to one phagocyte and the results were expressed as the percentage of viable intracellular bacteria.](image-url)
decreased in the iron-deficient group. The molecular basis of reduced microbicidal activity in iron deficiency is not clear, but decreased peroxidase activity and iodination may be contributory.

Serum immunoglobulin concentrations are within the normal range in iron-deficient subjects and increase after infection. The number of B lymphocytes and specific antibody responses to tetanus toxoid and S. typhi, and serum complement activity and levels, was also found to be comparable in iron-deficient and healthy children (10,11). Although salivary IgA level may be normal, specific IgA antibody to measles virus was reported to be reduced (8,19). These changes in immune responses occur early in the evolution of iron depletion (11,20). Similarly, in those with iron deficiency anemia, treatment with iron improves immunocompetence prior to increase in hemoglobin levels (16). These data suggest that reduction in tissue and cellular iron concentration and not the anemia is the primary cause of altered immunity associated with lack of iron.

The differences in the results of various studies on immune responses in iron deficiency may well be due to a number of confounding variables, including variations in methodology of various immunity function tests, e.g., dose of antigen or mitogen, or number of microorganisms (21,22). In some reports, the number of subjects examined was very small: 5 to 8 (13,14). A second important variable is the presence of concomitant or recent infection and parasitic disease. Thirdly, the cause of iron deficiency is a significant factor; reduced dietary intake of iron produces more prominent effects on immunity than deficiency resulting from blood loss, including hookworm disease. The diagnosis of iron deficiency is often suspect and appropriate controls may not be used.

Iron-Binding Capacity

The growth needs of microbes and animal cells for iron are similar. Bacteria have the ability to produce “siderophores,” such as phenolate or hydroxamate compounds, to solubilize and assimilate the metal (5). Fever, a host protective mechanism, suppresses the ability of pathogens to synthesize iron ligands. The control of iron concentration and temperature are widely employed in industry to modulate the amount of toxin and antibiotic formation in fermentation processes.

In vitro, the ability of added ionic iron to reduce the microbiostatic function of serum has been demonstrated with a variety of bacteria and fungi. Based on iron dependency for virulence and the nature of the infection produced, bacteria have been arbitrarily classified into four categories (23). Transferrin saturation in excess of 70% is generally necessary to achieve this effect, a condition rarely encountered in clinical practice. Lactoferrin present in large amounts in human milk may contribute to the anti-infective properties of breast milk, particularly in protection against enterobacterial diarrhea (24). Bacteriostasis achieved by lactoferrin is markedly potentiated by specific antibody (Fig. 4). This iron-binding compound may also have a bactericidal action (25).
Iron Status and Incidence of Infections

Observations in Humans

Studies on the incidence of infections in relation to iron status are difficult to control and conduct. One can fault most of the published literature on this topic on the grounds of inaccurate diagnosis (of iron deficiency and infection), retrospective analyses, inadequate controls, observer bias, and frequency of observations. However, it can be stated with confidence that iron supplementation within physiological needs to prevent anemia or in doses necessary to correct anemia may reduce, but certainly not increase, the risk of infection. Moreover, oral iron intake generally does not increase the availability of free iron that is necessary for bacterial multiplication.

Infection is the most common disease for which iron-deficient children seek medical advice. An Expert Group of the World Health Organization (26) commented that individuals with nutritional anemia tend to have more frequent infection. MacKay (27) observed a modest decrease in the number of episodes of bronchitis and gastroenteritis in iron-supplemented infants from low-income families in London. Andelman and Sered (28) found that respiratory infections were significantly less in infants who were given an iron-fortified milk formula. Other studies have not demonstrated any beneficial effects (29,30). A. Stekel and G. Heresi (personal communication) found decreased prevalence of diarrhea in some seasons in iron-supplemented infants. We have observed a reduced frequency of upper- and lower-respiratory infections in infants given iron supplements.

Iron deficiency and impaired cellular immunity are common findings in patients with chronic mucocutaneous candidiasis (31). The skin lesions as well as immunologic abnormalities reverse rapidly on administration of iron. Fletcher et al. (32) reported Candida albicans infection in the mouth lesions seen in iron-deficient individuals; the patients’ saliva supported fungal growth better than control samples.
A local factor, such as changes in microflora consequent to iron lack, was postulated to be important.

We have examined a group of medical students with recurrent herpes simplex infection and found a higher prevalence of iron deficiency in them compared with other students without herpes (Fig. 5). Moreover, the response of lymphocytes to herpes simplex antigen and tetanus toxoid improved significantly 4 weeks after oral iron therapy (Fig. 6) and was associated with clinical remission monitored over a period of 1 year.

**FIG. 5.** Transferrin saturation of individuals with recurrent herpes labialis and those without such history. A cutoff point of \( \leq 16\% \) defines iron deficiency.

**FIG. 6.** Lymphocyte stimulation response to tetanus toxoid and herpes simplex antigens in iron-deficient individuals before and after iron therapy.
The assertion that "iron deficiency protects against infection" is not supported by a critical analysis of observations. The data of one report (33) often cited as evidence for this hypothesis must be correctly viewed in detail. This study looked at the presence of infection on admission among 110 adults with hemoglobin less than 10 g/dl; of the 67 with severe iron deficiency or dimorphic anemia, five (7%) were diagnosed to have bacterial infection and 16 (24%) malaria. It was stated that the "malarial attacks in the iron-deficiency group usually developed after iron treatment was started." The workers concluded that, "the low frequency of bacterial infections in the iron-deficient group suggests that patients with iron-deficiency anemia are not as vulnerable to infections as has hitherto been suspected, but they are susceptible to malaria." These conclusions are not justified on the basis of the observations made. Firstly, no control group of nonanemic subjects was examined. What was being compared was the prevalence of infection among patients with different etiologic types of anemia. Secondly, those with positive bone marrow iron included patients with sickle cell disease and trait and other conditions known to change susceptibility to disease. Thirdly, the diagnosis of iron deficiency was based on blood and bone marrow smears; serum iron and transferrin saturation were not done. Fourthly, blood cultures to document bacterial infection were set up only in those patients (34 of 110) who had fever. It is well known that protein-calorie malnutrition present in many of the study subjects can suppress febrile response. In others, bacterial infection was diagnosed on the basis of response to antibiotics; the self-limited course of many infectious illnesses, especially viral, makes the therapeutic response an unsatisfactory diagnostic criterion. Similarly, malaria was diagnosed by demonstration of the parasite only in 6 patients; in the remaining 12, it was based on response to chloroquine. Also, the nature of iron supplements and their duration are not stated, and posttherapy data are provided for malaria but not for bacterial infections. The impact of other associated nutrient deficiencies (33 had swelling of the legs), protein deficiency, or a malarial nephrotic syndrome was not considered. These limitations detract seriously from the conclusions reached. Similarly, Murray's observations (36) that symptomatic disease was evident more often in Somali nomads after a period of iron supplementation may mean that the prevalence of clinical diseases in which cell-mediated immunity plays a role of clinical expression may be more apparent because iron therapy has improved cellular immunity, but these data do not imply that the incidence or the outcome of infectious illness is adversely affected by treatment of iron deficiency. Lack of documentation of infection, effects of season, overcrowding, and other variables present major difficulties in interpretation of these data.

Some reviews on the topic (35,36) have failed to emphasize these limitations of reported data, implying that iron deficiency in humans protects from infections, and thus have wavered on the question of iron status and susceptibility to infection.

Chronic iron overload, as in thalassemia and hemochromatosis, is not characterized by frequent infections. This is further supported by the observation that in vivo iron saturation of serum does not impair its bacteriostatic properties (6).
Observations in Animals

The infectious consequences of dietary iron deficiency have been evaluated in several animal models and the data have been reviewed (7,37,38). In young swine rendered iron-deficient and exposed to *E. coli* endotoxin, the 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. The susceptibility to infective challenge with *S. typhi* or *Strep. pneumoniae*, assessed by morbidity and mortality, was enhanced in iron-deficient animals. Preweaning 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 vulnerability to *S. typhi*. 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. For instance, the growth of nonpigmented mutants of *Pasteurella pestis* was enhanced by injections of iron. In an experimental mouse model, changes in iron status, secondary to administration of endotoxin or iron, mediated the susceptibility of animals to challenge with *C. albicans*. Thus the route of administration and the nature of iron compound used may be important in host-bacteria interactions. A recent report (39) describes the effect both of oral iron and intramuscular iron-dextran on incidence of pneumonia and diarrhea in calves. Iron-dextran administration reduced the frequency of anemia but oral iron produced a more distinct benefit than intramuscular therapy, the effect being more evident in the duration of pneumonia.

Iron Administration and Infection

A report of a high incidence of gram-negative septicemia in Polynesian newborn infants given a series of iron-dextran injections (40) has evoked concern about the use of iron in the prevention of iron deficiency in infants. However, newborns may have a relatively inefficient mechanism for dealing with large quantities of complexed iron. Macrophage blockade may impair host defense. The use of moderate doses of iron-dextran after the neonatal period did not predispose infants to infections (41). Certainly, the use of the conventional preventive or therapeutic doses of oral iron has not been associated with increased risk of infection; if at all, this may decrease such common illnesses as otitis, upper- and lower-respiratory infections, and diarrhea.

Children suffering from protein-calorie malnutrition present a special problem since they have reduced levels of iron-binding proteins (42), which correlate with chances of survival. Large doses of iron in the initial stages of nutritional management may predispose malnourished children to bacteremia and high mortality. However, this risk is minimized if iron administration is delayed by a few days, giving opportunity for repair of transferrin synthesis (Table 1).
TABLE 1. Timing of iron therapy and mortality in well-nourished and malnourished children with iron therapy

<table>
<thead>
<tr>
<th></th>
<th>After 72 hr of admission</th>
<th>Within 72 hr of admission</th>
</tr>
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<tbody>
<tr>
<td>Well nourished</td>
<td>2/50</td>
<td>1/41</td>
</tr>
<tr>
<td>Kwashiorkor</td>
<td>3/18</td>
<td>5/12</td>
</tr>
<tr>
<td>Marasmus</td>
<td>2/35</td>
<td>1/16</td>
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*Number of deaths/total number of patients.

GASTROINTESTINAL SYSTEM

Iron deficiency is associated with a variety of clinical manifestations pertaining to the gastrointestinal tract. These can be both the cause and the effect of iron deficiency. Histological studies have shown changes in epithelial morphology, including metaplasia of buccal and esophageal mucosae. Surface epithelial cells in tissues obtained from iron-deficient subjects have a reduced content of cytochrome and other enzymes. Hypo- and achlorhydria may occur. A few studies have shown variable dysfunction of absorptive processes, including reduced uptake of ingested D-xylose and of fat. Jejunal biopsies have revealed morphologic changes in villus structure and enzyme content in iron deficiency; the extent of such changes varied from mild to severe (43,44). In some patients, the investigations have been repeated after appropriate iron therapy and a partial or complete recovery of gastrointestinal structure and function was observed. Fecal occult blood is detected more often in iron-deficient subjects than in controls. Iron deficiency in young puppies and rats is associated with reduced activity of sugar-splitting enzymes, but the mucosal architecture is preserved (45,46). The subject of small intestinal structure and function in nutritional deficiency has been recently reviewed (47).

THERMOREGULATION

It has been reported that iron-deficient rodents cannot maintain normal core body temperature when stressed with cold, and that the conversion of T4 to T3 is impaired (48). The serum and urinary levels of catecholamines are increased. Iron deficiency alters mitochondrial electron transport systems both in adipose tissue and in brown fat. Body insulation is not changed since hair thickness is unaltered and cutaneous vasoconstriction is intact. Oxygen consumption at 4°C is reduced. Treatment with iron results in reversal to normal T3 levels in 1 week. The modulating influence of thyroid function in thermoregulation has been shown also by the observations that thyroidectomized iron-deficient rats injected with T3 do not show cold stress-induced hypothermia whereas T4 administration fails to prevent hypothermia and increases catecholamines at 4°C (48).
PHYSICAL WORK CAPACITY

Latent iron deficiency without anemia may be expected to alter cellular metabolism and tissue function by decreasing the availability of various iron-containing and iron-dependent enzymes and other proteins, including cytochromes, and mitochondrial enzymes for oxidative phosphorylation and energy production. Iron deficiency anemia leads to decreased oxygen delivery to the tissues, such as skeletal muscle. The effect of anemia would be obviously more pronounced in laborers doing physically demanding tasks than in domestic or sedentary workers. Decreased oxygen affinity and increased cardiac output are the adaptive physiological measures of the body in response to anemia. This adaptation can cover the metabolic needs of the body at rest or for sedentary work but it cannot cope with the metabolic needs of the body for work involving physical endurance.

In humans, physical work capacity studied by the Harvard step test has been shown to be proportional to the hemoglobin concentration of the subject (49). An analysis of work time, percentage of the people reaching the maximal work load, heart rate response to work, and postexercise blood lactate levels has led to the conclusion that anemic subjects have a lower work capacity than healthy nonanemic controls (50). Subjects with hemoglobin concentrations between 11.0 and 11.9 g/dl showed a 20% decrease in work tolerance when compared to those with levels above 13.0 g/dl. In a study carried out in Indonesia on rubber plantation workers it has been shown that anemia, even at the high cutoff level of 13.0 g/dl, affected a worker's ability to perform the Harvard step test (51). Income from rubber tapping was directly proportional to the hemoglobin concentration. Treatment with ferrous iron and a small incentive payment resulted in improved work output and hence productivity. Our data corroborate such findings relating anemia to physical work capacity (Fig. 7). Furthermore, we differentiated the ability to perform short bursts of activity from endurance; the latter was affected much more in iron deficiency (Fig. 8). Work performance may increase as early as 4 days after initiation of iron treatment (52). A significant improvement in the productivity of

![Graph](image-url)

**FIG. 7.** Physical work performance related to the presence of anemia. The differences were more marked as the duration of work increased. (From Chandra and Vyas, ref. 2.)
Iron-deficient workers on a tea plantation was observed after 3 weeks of iron supplementation (53).

Animal studies support such observations. Finch et al. (54), using iron-deficient rats, have shown that work performance increased fivefold after 3 days of iron treatment prior to any detectable change in hemoglobin levels. Iron-deficient rats had lower exhaustive run time, elevated heart rate, and cardiomegaly (55).

These data suggest that iron deficiency anemia is related to decreased work capacity, leading to reduced productivity and poor individual income, which may aggravate the problem further by worsening undernutrition and consequent enhanced morbidity and mortality. Anemia per se reduces work capacity but improvement in this function after iron supplementation for a short period suggests that not only hemoglobin concentration but changes in tissue enzymes secondary to iron deficiency, e.g., α-glycerophosphate oxidase, and the resulting lactic acidosis also may be important in iron-deficient subjects.

COGNITION AND BEHAVIOR

In laboratory animal studies, iron deficiency has been shown to cause fetal resorption and decrease in body size and weight. Rats deprived of iron during early life have reduced amounts of nonheme iron in the brain, with behavioral and physiological consequences (56). Mackler et al. (57) have shown that the specific activity and tissue concentration of enzymes of oxidative phosphorylation in mitochondria from the brain were unaffected by iron deficiency while aldehyde
oxidative activity was decreased. There was an accumulation of serotonin and 5-hydroxyindol compounds. Iron treatment restored the level of the enzymes and neurotransmitters to the normal range. Serotonin and tryptaminergic drugs have been reported to produce drowsiness and decreased attentiveness and ability to learn. Thus, it has been postulated that iron deficiency may lead to defects in cognitive development and function. There are several reports documenting impaired mental functions in iron-deprived animals and human subjects. Massaro and Widmayer (58) have shown that iron deficiency anemia in rats adversely affected some aspects of associative learning. Howell (59) reported that 3- to 5-year-old iron-deficient children with hemoglobins less than 10 g/dl showed decreased attentiveness, narrow attention span, and perceptual restriction. Sulzer et al. (60) have shown that anemic children of 4 to 5 years of age with hemoglobins less than 10 g/dl were poor in a vocabulary test, had lower IQ measures, and showed impaired performance in measures of the latency and associative reactions. Iron deficiency has adverse effects on attention and memory control processes, which return to normal after iron treatment. Iron-deficient young adolescent subjects were also shown to score comparatively lower on tests of academic performance—which included vocabulary, reading knowledge, use of reference material, arithmetic concepts, and problem solving—and were, moreover, found to be more disruptive, irritable, and restless in the classroom than other students. Oski and Honig (61) have shown that mental and developmental scores in infants 9 to 26 months old with hemoglobins less that 10.5 g/dl improved after iron treatment for 6 to 8 days. In addition, iron treatment also resulted in improved gross and fine motor coordination. Others did not find any relationship between IQ measures and degree of anemia among children (62), but the type of anemia investigated was of the hemolytic variety observed in sickle cell disease in which iron deficiency may not be seen. A recent report by Lozoff et al. (63) concluded that developmental deficits assessed by the Bailey method are more frequent in anemic children than in nonanemic controls and that there was little improvement after short-term oral iron therapy. The lack of improvement may be due to the need for long-term therapy, as seen also in experimental animals. Perhaps the cause of lower developmental scores in anemic children may be an intervening variable closely linked to iron deficiency; lead toxicity could be considered one such factor. Pollitt and Leibel (64) state that "it is unclear whether the poor performance, perceptual disturbance and conduct problems observed in anemic subjects were consequences of anemia, per se, of iron deficiency alone, or of a general nutritional inadequacy."

Iron deficiency may occasionally be associated with behavior disorders, such as pica, pagophagia, breath-holding spells, and temper tantrums (65,66). Abnormal eating behavior may both be the cause or the effect of iron deficiency. Iron therapy has been observed to accelerate the cessation of these generally self-limited aberrations of behavior.

The interesting results of these studies on iron deficiency and behavioral development suggest that iron is a critical element for the normal functioning of the central nervous system. Many methodologic problems, however, plague studies on
this topic, not the least of which is the reliability of the testing procedures for young children; others are the problems of crosscultural transfer of techniques, retrospective analyses, inadequate controls, and definition of iron deficiency. Several investigations in progress are attempting to use improved assessment methods and should provide much-needed answers to the question of the effect of iron deficiency on cognitive ability and behavior.

REFERENCES