THE LIABILITIES OF IRON DEFICIENCY

Iron has been recognized as a potent hematonic since the inception of hematology as a clinical discipline. Even ancient civilizations believed in the beneficial effects of medicinal iron. Nevertheless, the precise functional liabilities of iron lack remain the subject of continuing debate. The consequences of iron deficiency, particularly from a socioeconomic standpoint, are especially important in light of its high global prevalence. A recent review of the literature indicates that ~30% of the estimated world population of nearly 4.5 billion are anemic, and at least half of these, 500 to 600 million people, are believed to have iron deficiency anemia.

FROM BOTH a clinical and a laboratory standpoint, iron deficiency is usually recognized by the anemia that accompanies its later stages. It is therefore hardly surprising that the liabilities of iron deficiency are often viewed only in terms of a decrease in circulating hemoglobin. Although one of the most important functions of iron is its role in oxygen transport and storage, iron participates in a wide variety of biochemical processes, including mitochondrial electron transport, catacholamine metabolism, and DNA synthesis. Not surprisingly, a broad spectrum of biochemical abnormalities resulting from iron deficiency has been described.

A large number of enzymes are known to contain iron or require it as a co-factor, including cytochrome oxidase, succinate dehydrogenase, aconitase, catalase, myeloperoxidase, cytochrome C reductase, ribonucleotide reductase, tyrosine hydroxylase, and xanthine oxidase. Although it has been difficult to relate the tissue concentrations of these enzymes to the functional consequences of iron deficiency, a depletion in tissue iron may be as important as a reduction in circulating hemoglobin.

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In certain infections, the role of mild iron deficiency is more evident. Iron deficiency is recognized as an important predisposing factor in chronic mucocutaneous candidiasis. Higgs and Wells reported that 23 of 31 patients with this disorder showed evidence of mild iron deficiency that was confirmed in most cases by bone marrow examination. This striking association may be explained in part by the impairment in epithelial function and structure that is known to occur in persons with mild iron deficiency and may also account for the recently described association between iron deficiency and recurrent Herpes simplex infection. A significantly higher prevalence of iron deficiency as measured by transferrin saturation was observed among medical students with Herpes infection as compared with a group of healthy controls.

The beneficial effect of iron therapy in reducing the incidence of mild infections apparently results from the correction of a defect in immune function. Whereas humoral immunity is normal in patients with iron lack, a defect in cell-mediated immunity has been demonstrated repeatedly. One of the earliest such observations was made by Joyson and co-workers, who described an impairment in lymphocyte transformation and migration inhibition factor production on stimulation with Candida antigen and purified protein derivative in 12 subjects with iron deficiency anemia. Both the proportion and the absolute number of circulating T cells are commonly reduced in patients with iron deficiency anemia. Lymphocyte proliferation and response to the mitogens phytohemagglutinin (PHA) and concanavalin A are impaired even in nonanemic patients with latent iron deficiency, and a significant correlation has been established between the lymphocyte stimulation index and transferrin saturation. In a recent study in ten iron-deficient children aged 12 to 30 months, the mean stimulation indices for Candida antigen and purified protein derivative in 12 subjects with iron deficiency anemia. Both the proportion and the absolute number of circulating T cells are commonly reduced in patients with iron deficiency anemia. Lymphocyte proliferation and response to the mitogens phytohemagglutinin (PHA) and concanavalin A are impaired even in nonanemic patients with latent iron deficiency, and a significant correlation has been established between the lymphocyte stimulation index and transferrin saturation.

In at least one clinical situation, heavy iron administration is associated with the development of serious infection. During the early 1970s, newborn Polynesian infants were given prophylactic intramuscular iron dextran in an effort to reduce the incidence of iron deficiency anemia. During the 5-year period of this program, the incidence of neonatal sepsis in the infants given iron was 11 in 1,000 total births as compared with 0.6 in 1,000 in European infants, a dramatic 20-fold difference. When this program of routine parenteral iron administration was stopped, the incidence of gram-negative neonatal sepsis fell from 17 to 2.7 in 1,000 births. Sepsis resulting from prophylactic iron was almost invariably due to *Escherichia coli* and occurred in >80% of cases between day 4 and day 10 following iron administration. Several factors may have accounted for the pronounced increase in neonatal sepsis. For example, infection may have resulted solely from administration of a deep intramuscular injection in the newborn, or reticuloendothelial cell blockade may have been produced by the iron dextran complex.

Nevertheless, the sudden influx of iron into the circulation and tissues in a nonphysiological form cannot be excluded as the primary predisposing cause. Iron dextran remains in the circulation for several days following intramuscular injection and provides a source of iron not otherwise available to microorganisms. In addition, the iron released from the iron dextran complex reduces the level of unsaturated circulating transferrin and could thereby impair the bacteriostatic properties of the plasma against *E. coli*. Whatever the cause, this report indicates that parenteral iron should not be given to newborn infants prophylactically. At the same time, there is no evidence that parenteral iron is hazardous to healthy persons with a competent immune system. Hundreds of women have been given parenteral iron during pregnancy with no recorded evidence of an increase in bacterial sepsis.

The hypothesis that iron deficiency may serve as a useful defense mechanism by withholding iron from bacteria, fungi, or protozoa has gained some tenuous support from recent studies in which iron was supplied to severely malnourished populations. One commonly cited report is that of Masawe and co-workers in which 100 anemic patients consecutively admitted to an adult medical ward in East Africa were studied for the frequency of infection. Approximately two-thirds of them had absent iron stores, whereas the remainder with storable iron had megaloblastic, hemolytic, or refractory anemia. It was noted that only 7% of the iron-deficient patients had bacterial infections, whereas between 64% and 83% with storable iron had various bacterial infections. Although it was suggested that the iron-deficient state protects against the development of bacterial infections, these observations could also be explained by the more common occurrence of infections in anemic patients with normal or increased levels of body iron, such as those with sickle cell anemia or bone marrow failure. For example,
hemolysis may promote bacterial growth by increasing iron supply in the form of heme compounds.\(^9\) The only proper control subjects in a study of this kind would be patients with normal hemoglobin levels.

These same workers reported that 16 of 18 patients with malaria, proven by the identification of *Plasmodium falciparum*, had iron deficiency anemia and noted that malarial attacks occurred commonly in these patients following the institution of iron therapy. Evidence shows that iron therapy may predispose to the development of malaria in other population settings. Following treatment of iron deficiency in Somali nomads, a recrudescence of malaria was observed in 13 of 71 persons as compared with only 1 of 76 in a control group.\(^28\) This phenomenon may be explained by an increased production of reticulocytes following iron therapy, with a resulting increase in malarial parasitemia. If the susceptibility to malaria is a consequence of reticulocytosis following iron therapy, a strong argument exists for the eradication of nutritional iron deficiency through programs of food iron fortification, thereby reducing the need to treat severely iron-deficient persons with medicinal iron.

It should be emphasized that these studies provide no evidence of a risk in treating iron deficiency in otherwise healthy populations or in persons who are not at risk for malarial infection. Further carefully controlled epidemiologic studies are needed to define the risk of alleviating iron deficiency anemia in severely malnourished populations. Because iron deficiency anemia in the tropics leads to severe morbidity and is frequently fatal, a noted authority in tropical medicine and hematology has concluded that severely anemic patients should be treated with iron while being protected against malaria and be treated for bacterial infections as they arise.\(^39\)

**WORK PERFORMANCE**

A significant limitation in certain types of physical activity has emerged as one of the most important consequences of chronic iron deficiency. This is certainly true from a socioeconomic if not a clinical standpoint. Interest in this facet of iron deficiency arises from studies in chronically anemic agricultural laborers engaged in physically demanding tasks in the lowlands of Guatemala.\(^30\) When a large group of men were tested for their ability to perform near-maximal exercise of brief duration (Harvard Step Test), a striking correlation was demonstrated between mean hemoglobin concentration and this aerobic activity. The key finding was not that the severely anemic person had a limitation in exercise performance, but that this was also related to differences in hemoglobin levels within the normal range. When iron and folate acid were supplied to the anemic men, a progressive improvement in exercise performance was observed, attaining a maximum after 2 months of treatment. The difference was highly significant when the men were compared with a control group, although a slight improvement was observed in control subjects as well, due to a training effect. This study provided the first solid evidence that even mild degrees of iron deficiency can impair performance in occupations requiring a heavy energy expenditure.

Similar findings have been observed in other field settings and with other types of work activity. Physical work capacity was studied in 75 female subjects employed on a tea plantation in Sri Lanka.\(^31\) Approximately two-thirds of them were anemic, with hemoglobin concentrations as low as 6 g/100 mL. Work performance was evaluated in a laboratory setting using a multistage treadmill test in which the percentage of grade was progressively increased at 3-minute intervals until a maximum possible work time of 18 minutes was attained. Performance improved at higher hemoglobin concentrations, both in total time on the treadmill and the percentage of persons reaching the highest workload. In addition, there was a striking correlation between mean hemoglobin concentration and the percentage of increase in mean heart rate when compared with values observed in subjects with a normal hemoglobin concentration \((r = .97)\). As in the Guatemala studies, even mild anemia (hemoglobin concentration between 11 and 11.9 g/100 mL) was associated with a 20% decrease in work tolerance. The postexercise lactate level was also sharply higher in anemic women and correlated closely with the degree of anemia. The authors concluded that because of the dramatic impairment in work capacity and an inferred reduction in work productivity, a strong case could be made for the correction and prevention of iron deficiency on the basis of economic as well as health considerations.

These observations were translated into concrete economic terms by studies in latex tappers employed on an Indonesian rubber plantation.\(^14\) Three hundred two male subjects aged 16–40 years were evaluated; 45% were anemic as judged by a hemoglobin level <13 g/100 mL. Hookworm infection was documented as the cause of the iron deficiency anemia in most subjects. Work output could be measured precisely in this study because each man was paid daily on the basis of the weight of latex he collected. Hemoglobin concentrations over the range of 10 to 16 g/100 mL correlated closely with income \((r = .56)\). The daily latex output was 18.7% lower in anemic men; when they were given 100 mg elemental iron each day for 60 days, their take-home pay increased by 37%. The relevance of these findings was less than clear-cut because an improvement also occurred in anemic men given a placebo. The cash incentive that had been provided to encourage participation in the study and that enabled the placebo group to purchase additional food was believed to explain the improvement in both hematologic status and work performance. This conclusion was supported by follow-up studies 45 days after iron supplementation was terminated. The anemic men who improved with the placebo had again become anemic, with an attendant decline in work output, whereas those given the iron supplement maintained the improvement in both hematologic status and work performance. The design of the study permitted the benefit/cost ratios based on the predicted yearly increase in latex collected and the cost of iron administration. The calculated ratio of 260:1 underscores the economic importance of eradicating iron deficiency in developing countries.

Further support for the contention that the correction of iron deficiency enhances work output of the sustained endurance type was furnished by studies on a tea plantation in Sri Lanka.\(^32\) As in the Indonesian study, work output could be
measured precisely by weighing the quantity of tea collected each day. Compared with a placebo group, women given iron supplementation for 1 month picked significantly greater quantities of tea, and the degree of improvement in work output was directly related to the severity of the original anemia. An intriguing observation relating to voluntary physical activity was also made in this study. The level of activity during 24 hours was recorded electronically, using a small sensing device strapped to the ankle of each subject. Following iron therapy, a progressive increase in daily physical activity was observed. It became statistically significant during the third week of iron replacement. The improvement in physical activity may have resulted from alleviation of the symptoms of tiredness and weakness commonly attributed to iron deficiency.

Limitations in work performance have traditionally been attributed to the attendant anemia rather than to the metabolic consequences of tissue iron deficiency. The results of animal studies conducted by Finch and co-workers, however, indicate that a deficit in tissue iron is also important. A treadmill was used to measure the work performance of normal and iron-deficient rats. The hemoglobin concentration in the two groups was adjusted to identical levels immediately prior to testing to eliminate the effects of anemia. The iron-deficient rats showed a marked impairment in running ability and a significant improvement in performance 24 hours after iron administration. The defect was fully corrected within 4 days, indicating that the metabolic abnormalities imposed by iron deficiency are rapidly reversible.

Published studies of work performance in a field setting do not distinguish between the consequences of anemia and tissue iron deficiency. A recent study in women athletes suggests, however, that the hemoglobin level is not the major deficit in chronic iron deficiency.1 In this report, the effect of 2 weeks of iron therapy on exercise performance and exercise-induced lactate production was measured in trained athletes. Although performance measured on a bicycle ergometer was unchanged after iron therapy, blood lactate levels at maximum exercise decreased significantly from 10.3 to 8.4 mmol/L in the iron-deficient women following therapy (P < .03). These observations were interpreted as evidence that iron plays an important role in oxidative metabolism and that iron-depleted muscles call on anaerobic metabolism for energy needs, with greater lactate production. Dallman has emphasized the importance of differentiating brief intense activity that relates to oxygen delivery and the concentration of circulating hemoglobin from prolonged endurance tasks that depend to a greater extent on muscle oxidative capacity.2 Further studies of work performance are needed to provide a clearer understanding of these separate deficits in persons with iron deficiency.

NEUROLOGICAL FUNCTION

Poor scholastic performance as well as chronic fatigue and other nonspecific symptoms have often been attributed to iron deficiency. Unfortunately, in many of the earlier studies, especially those in children, it has not been possible to distinguish the effects of iron deficiency from other factors such as nutritional and social deprivation.45 Furthermore, tests used to evaluate mental development in children are relatively crude, making it difficult to isolate the component attributable to iron lack. Because symptoms in adults are largely subjective, it has been difficult to differentiate true responses to iron from placebo effects.

Despite these limitations, a pattern of age-related neurological dysfunction appears to be emerging from the results of several more recent carefully controlled investigations. Most of them involve children. This literature has been reviewed recently46,47 and an exhaustive evaluation of all the related publications will not be given here; rather, an attempt will be made to develop the common theme that is evident in the newer studies. Only sensory and behavioral disturbances have been recorded consistently; motor function is usually normal. Moreover, several different observations point to a primary abnormality in the ability of iron-deficient children to direct attention to a specific task and suggest that other apparent neurological deficiencies may be a consequence of this primary neuropsychiatric dysfunction.

Most investigators have selected a relatively small age range to study. It is convenient to consider their findings in terms of four age groups: infants (0 to 2 years of age), preschool children (3 to 6 years of age), school children (6 to 12 years of age), and adults.

Infants. The assessment of mental development and performance in this age range is particularly challenging. The Bayley Scales of Infant Development (BSID) is the tool that has been used most widely to measure differences between iron-deficient infants with or without anemia and their iron-replete counterparts. The BSID gives a comprehensive and carefully standardized assessment of developmental status between the ages of 3 and 30 months of age.48 It consists of three complementary parts: the mental development index (MDI), which evaluates sensory-perceptual acuity and discrimination; the motor scale, which provides an assessment of body control and coordination of both large and small muscle movements; and the behavior record (IBR), which is a measure of the infant’s social and objective orientation to the immediate environment. Although the BSID is extremely useful, it is difficult to administer optimally and is heavily dependent on the experience of the examiner. Moreover, when comparisons between numerous elements of the test are made, the probability of finding a significant difference in isolated elements by chance alone is increased, especially when one considers the rapid developmental changes occurring during infancy.37 There is also a lack of continuity in performance, demonstrated by a poor correlation between test and retest scores separated by months. Longitudinal comparisons between treated and untreated experimental groups must therefore be carried out in a short time that may be insufficient to demonstrate the corrective effects of iron administration.

Despite these methodological handicaps, impaired attention span and cognitive developmental abnormalities have been reported with surprising consistency in studies in which infants at or near 2 years of age have been included in the sample. Indeed, apparent discrepancies between different
reports in the literature may be a reflection of the age group studied. Deinard and co-workers used three tests, a visual habituation measure, the BSID, and the Uzigris and Hunt Ordinal Scales (I, II, IV) of Psychological Development, to evaluate nonanemic children aged 11 to 13 months with ferritin values of either <9 ng/mL or >20 ng/mL. This is a relatively small variation in iron status, and there were no differences in overall performance between the two groups. On the other hand, when 37 15-month-old infants were studied by Walter and colleagues, values for the BSID MDI were found to be significantly lower in children with iron deficiency anemia than in carefully matched controls, although both groups fell within the normal range for American children. Oral iron therapy (3 to 4 mg iron per kilogram per day) returned the MDI for iron-deficient infants to control values in 10 to 15 days and was without effect on the control infants. An improvement in cooperativeness and attention span on the BSID was also noted. A similar rapid improvement in cognitive function has been reported by Oski and Honig after iron-deficient anemic infants with a mean age of 16 months were given treatment of 5 to 8 days of intramuscular iron. Finally, Lotzoff and colleagues demonstrated the presence of a relationship between age and the detectable effects of iron deficiency in a single study of infants aged 6 to 24 months. When the infants were analyzed in three groups (6 to 12 months, 13 to 18 months, and 19 to 24 months), a significant decrease in the MDI with iron deficiency occurred only in the oldest age group. Furthermore, there was a significant positive correlation between iron status and MDI in the latter group.

Although these observations suggest that detectable abnormalities of neurological functions related to iron deficiency appear only in later infancy, the explanation is not immediately evident. Several possible reasons have been put forward. It may be an artifact of the method of evaluation. The BSID shifts from an emphasis on motor development at 12 months to more verbal and cognitive skills at 24 months. Only sensory, cognitive, and behavioral abnormalities have been observed. With few exceptions, normal motor function has been reported. On the other hand, the duration of iron depletion or the stage of neurological development at which it occurs may be important. It is equally possible that other factors unrelated to iron nutrition may play a role.

Preschool children. Abnormalities similar to those reported in older infants have been observed in preschool children. Pollitt and co-workers studied 15 children with mild iron deficiency and 15 controls aged 3 to 6 years. The two groups performed equally well on the Stanford-Binet Intelligence Test and an oddity learning task. Iron-deficient children took more trials to achieve the required level of proficiency in three discriminatory learning tasks, however. Nevertheless, when presented immediately with the reverse problem (the previously incorrect stimulus was now correct), the two groups showed no differences, demonstrating satisfactory short-term memory. On the other hand, there was a significant decrease in performance when a separate, simple, short-term memory test was administered de novo. The authors interpreted their findings as consistent with a deficit in directing attention rather than a true learning rate deficiency. Differences in discrimination learning but not those related to the short-term memory test disappeared after 4 to 6 months of iron therapy. This study is somewhat compromised by suboptimal documentation of iron status and reassignment of subjects between the control and study groups. Nevertheless, the observations are intriguing and similar to others recently reported from Guatemala.

School children. Poor scholastic performance, disturbances in attention and perception, and unsatisfactory conduct were reported in early studies carried out by Webb and Oski among 14-year-old high school students living in an economically deprived community in Philadelphia. Unfortunately, methodological problems and the possible contribution of other nutritional as well as concommitant social factors preclude conclusive inferences from these investigations. The most complete study was undertaken recently in Indonesia. Seventy-eight 11-year-old children who met strict criteria for iron deficiency anemia were compared with 41 carefully matched nonanemic controls. A neurological evaluation was performed before and after the supervised administration of ferrous sulfate or placebo for 3 months. Once again, a deficit in directing attention appeared to be the primary abnormality.

The Borden-Wisconsin test for concentration, a measure of attention maintenance, was significantly improved after iron administration in anemic children, but not in the group given placebo or in the nonanemic children given iron. Raven Progressive Matrices IQ Scores of anemic and nonanemic children were not significantly different. Scholastic performance as measured by a modified standard achievement test was significantly better in nonanemic children, however; iron therapy led to an appreciable improvement, although the performance of the anemic children was still significantly lower than that of the nonanemic controls at the end of 3 months. The authors again considered the primary abnormality to be one of directing attention with a secondary effect on scholastic achievement. The deficit in academic performances may require a >3-month period for complete correction. Unfortunately, the possible long-term consequences of childhood iron deficiency on adult academic achievement are unknown.

Adults. Clear evidence of an association between iron deficiency and psychological or cognitive function in adults has not been obtained, although Tucker and colleagues found preliminary evidence for a positive correlation between serum ferritin concentration and verbal fluency as well as electroencephalographic asymmetry. Higher ferritin values were associated with poorer nonverbal auditory task performance, however. Chronic fatigue and other nonspecific symptoms were reported to respond to iron therapy in some persons in one study, but other investigators have produced conflicting results.

The only sensory disturbance that has been documented clearly in adults is a perversion of taste leading to the consumption of non-food items (pica). A commonly encountered form in the United States is pagophagia or compulsive ice eating. Indeed, this was the only nonhematological manifestation of iron deficiency detected by Rector and co-workers in seven patients in whom regular phlebotomy...
for polycythemia vera had produced chronic iron deficiency. The craving for ice appeared to be specific. It could not be attributed to stomatitis or glossitis and was not satisfied by cold liquids or ice cream. Pagophagia is rapidly cured by doses of iron less than those required to correct anemia or repair the iron-storage deficit. Various forms of pica have been observed in several parts of the world. It occurs at all ages but is most frequently encountered in children and pregnant women. Although pica appears to be a valid symptom of iron deficiency in many circumstances, several of the substances consumed adsorb iron and inhibit its absorption, thus contributing to the deficiency state. Moreover, there may be other causes of pica itself. For example, ash eating is common among South African black women who are not often iron deficient.

In summary, there is an increasing body of evidence connecting iron deficiency with or without anemia with deficits in attention span leading to learning and problemsolving difficulties in children. The neurophysiological mechanisms involved are still largely speculative. Several parts of the brain contain large quantities of iron, and iron is required for the activity of enzymes such as tyrosine hydroxylase, tryptophan hydroxylase, and monoamine oxidase that are important to amine neurotransmitter metabolism. A series of studies in rats carried out by Youdim and colleagues suggests that dopamine receptor function is impaired in iron deficiency and leads to the observed neuropsychological changes.

No information implicates academic or social handicaps in adults with iron deficiency during childhood or the later years, but it seems likely that impaired learning could have important consequences for the person's subsequent achievement in a world of increasing technological complexity. The insidious but potentially far-reaching consequences both for the individual and the community, particularly in developing countries where iron deficiency is still a prevalent nutritional disorder, should not be ignored. Although our understanding of the neuropsychological consequences of iron lack is undoubtedly fragmentary at this time, the studies outlined above provide ample reason for concern and a convincing rationale for programs to ensure adequate iron nutrition in the growing child.

CONCLUSIONS

The key nonhematologic liabilities of iron deficiency in humans relate to abnormalities in host defense, work performance, and neurological function. The relationship between iron status and infection remains highly controversial. A defect in cell-mediated immunity and neutrophil function can be readily demonstrated in iron-deficient patients and may predispose to common respiratory or diarrheal infections. On the other hand, evidence shows that vigorous iron therapy may enhance the risk of certain overwhelming infections, especially in the immunocompromised host. In several field trials, alleviation of iron deficiency has led to an increase in work output of the sustained endurance type, a finding that has important socioeconomic implications in developing countries. With regard to neurological function, the most important defect appears to be an impairment in attention span and cognitive development that has been demonstrated in late infancy, preschool, and school-age children. This defect in learning ability could have far-reaching consequences in areas of the world where iron deficiency remains a common nutritional problem.

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