Review

Functional Consequences of Iron Deficiency in Human Populations

Nevin S. Scrimshaw

Institute Professor,
Massachusetts Institute of Technology,
Cambridge, Massachusetts, U.S.A.

(Received November 19, 1983)

The widespread occurrence of iron deficiency in developing countries is now well documented. Its high prevalence in these countries is attributable not only to the poor availability of iron in diets because of high fiber and phytate content, but also to chronic blood losses due to hookworm, schistosomiasis, and malaria (1). A high prevalence of iron deficiency anemia obviously means an equal or greater prevalence of iron deficiency not severe enough to cause anemia. If it should be demonstrated that subclinical iron deficiency has functional consequences, the significance of iron deficiency for these countries is even greater than has been recognized. There is growing evidence, as reviewed in this paper, that this is indeed the case.

In fact, some of the first evidence for this came from a study of preschool children in Cambridge, Massachusetts that failed to find anemia in this population. However, it demonstrated that iron deficiency per se, as diagnosed by levels of serum iron, ferritin, and transferrin saturation, was sufficient to affect this performance on some cognitive tests (2). This has led to a broader search for the functional consequences of iron deficiency to include subclinical as well as clinical iron deficiency. While neither iron deficiency nor iron deficiency anemia is limited to developing countries, prevalence rates are highest for women of childbearing age, but are by no means limited to this group.

There has been a great deal of recent research on the availability of dietary iron in various kinds of diets, on practical ways of fortifying staple food and diets, and on the prevalence of iron deficiency anemia in various populations. To complement such studies, the United Nations University has established a network of institutions in developing countries to investigate the functional consequences of iron deficiency. Extensive work is under way in Egypt, Thailand, Chile, and Indonesia, and additional studies are planned. While the results of these studies are not yet available, there is already evidence that iron deficiency impairs resistance to infection, cognitive performance, physical capacity, work output, and possibly even maintenance of body temperature. This paper will review and evaluate the currently available evidence.

The total amount of iron in the body of a 70 kilogram man is about 3.5 g, of which 70% is contained in hemoglobin. Other iron compounds constitute a very small percentage of the total, and are located primarily in solid tissues. Myoglobin accounts for about 4% of the total, and most of the additional iron is present in a large number of oxidative enzymes, including mitochondria, cytochromes, and flavoproteins. While these latter account for only a minute fraction of the iron in the body, they fulfill...

1 Presented at the 37th General Meeting of the Japanese Society of Nutrition and Food Science, Osaka, Japan, May 8, 1983.
important functions. Myoglobin is involved in the transport of oxygen across the muscle cells and is stored in muscles. Cytochromes, flavoproteins, and other mitochondrial iron compounds play an essential role in the oxidative production of cellular energy as ATP. Since muscular exercise in work involves large expenditures of energy and markedly increases oxygen consumption over resting levels, it is not surprising that iron deficiency can result in impaired work performance and affect behavior.

In studying the effects of iron deficiency, three overlapping stages must be taken into account. First, the loss of storage iron, as reflected by a decline in the serum ferritin concentration, and second, a decrease in circulating iron, characterized by a decline in serum iron and a rise in the iron-binding capacity, best expressed as a ratio between the two, the transferrin saturation. The third stage occurs when the production of essential iron compounds, including hemoglobin, is restricted. Experimental and field studies that I will describe indicate that even the mildest of these stages may, under some circumstances, have significant functional consequences.

Iron Deficiency and Work Performance

The rat has been used to investigate the degree to which various types of work performance are impaired by anemia and by the associated decreased activity of iron-containing enzymes and iron-dependent enzymatic reactions. Despite the quantitative differences between iron metabolism in the rat and man, the progression of iron deficiency and the interrelationships of various biochemical manifestations are qualitatively similar.

Edgerton and co-workers, in 1972, reported that animals put on an iron-deficient diet near the time of weaning and made anemic by bleeding or by administration of phenylhydrazine all showed a strong relationship between concentration of hemoglobin and running time to exhaustion (5). Running time returned to control values within 3 to 4 days of iron treatment. In another experiment, shown in Fig. 1 (6), severity of anemia and the percent decrease in spontaneous activity were closely correlated in young rats made anemic by bleeding. Finch and co-workers (7) gave iron-deficient diets to male Sprague-Dawley rats at 4 weeks of age and compared them at 8 weeks with control animals on a normal diet and with rats on the iron-deficient diets but given weekly injections of iron. As shown in Fig. 2, the iron-sufficient animals on a normal diet and those on the iron-deficient diet with added iron had mean treadmill running times of 17 and 20 min, respectively. Animals that were iron-deficient but transfused showed no significant improvement in their original running time of about 3 min. After three days of iron treatment, however, the running time of the iron-deficient rats improved. Similar studies by Davies, Finch and co-workers, and Askew and co-workers confirm these adverse effects of an iron-deficient diet on various intensities of treadmill exercise and indicate that anemia is only one factor in this effect (8–10). In these studies transfusion that corrected the anemia did not restore running time.

Metabolic changes in the skeletal muscle of iron-deficient rats in these studies were decreased concentrations of iron-containing enzymes and proteins, including cytochromes, myoglobin, mitochondrial and oxidative enzymes that serve important physiological functions. These biochemical abnormalities are accompanied by impairment in performance of several types of exercise. Reversal of these
effects was most closely correlated with increasing activity of alpha-glyceryl phosphate oxidase in one group of studies (7) and with pyruvate malate and succinate in another (10).

I first came to appreciate that these studies in animals have important parallels in human populations during a 1970 field study on a mixed coffee and sugar plantation on the Pacific coast of Guatemala, in which we found a marked decrease in the Harvard Step Test performance of anemic workers. These were also individuals regarded by the plantation owner and his foreman as poor workers, and they considered them lazy and stupid. With iron supplementation, not only did their Harvard Step Test performance return to normal, but also they were observed to become more willing, intelligent, and effective workers.
Fig. 5. Changes in Harvard Step Test score (HST score) in two groups of Guatemalan agricultural workers before and after 4 months of treatment with placebo or with oral iron (Viteri, 1976 (11)).

Table 1. Maximal predicted work load sustained by individuals with various levels of hemoglobin concentration (cal/min).

<table>
<thead>
<tr>
<th>HGB concentration (g/100 ml blood)</th>
<th>Maximal work load for maximal cardiac output</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>4.8</td>
</tr>
<tr>
<td>8</td>
<td>6.4</td>
</tr>
<tr>
<td>10</td>
<td>8.0</td>
</tr>
<tr>
<td>12</td>
<td>9.6</td>
</tr>
<tr>
<td>14</td>
<td>11.1</td>
</tr>
<tr>
<td>16</td>
<td>12.7</td>
</tr>
</tbody>
</table>

(Viteri, 1976 (11)).

Table 2. Difference in Harvard Step Test scores of anemic and non-anemic workers ($p < 0.01$).

<table>
<thead>
<tr>
<th></th>
<th>Rentang</th>
<th></th>
<th>Saladarma</th>
<th></th>
<th>Halim</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anemic</td>
<td>Non-anemic</td>
<td>Anemic</td>
<td>Non-anemic</td>
<td>Anemic</td>
<td>Non-anemic</td>
</tr>
<tr>
<td>No.</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>HGB</td>
<td>8.6</td>
<td>15.2</td>
<td>8.7</td>
<td>15.6</td>
<td>8.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Score</td>
<td>64</td>
<td>82</td>
<td>51</td>
<td>74</td>
<td>39</td>
<td>76</td>
</tr>
</tbody>
</table>

(J. Nutr. Sci. Vitaminol.)
shown in Fig. 6, when take-home pay of the rubber tappers was used as an indication of their work output, there was a linear correlation with hemoglobin level. There was also a difference in the frequency of absences due to diarrheal, respiratory, and other infectious disease between anemic and non-anemic workers.

An intervention study was then designed in which half of each group, anemic and non-anemic, was supposed to receive 100 mg of elemental iron per day for 60 days, and the other half, randomly selected, a placebo. The results of the supplementation were striking. Table 4 shows that the Harvard Step Test scores returned to normal. The take-home pay of the rubber tappers increased 37%, and there was a decrease in morbidity from infectious disease. As indicated in Fig. 7, there was even a 15% increase in the area weeded by the weeders, although they did not gain from this. Al became tired after 5 h and the difference between the two groups was no longer seen.

To everyone's surprise, however, there was also a marked improvement in all of the values for the anemic group receiving only a placebo. It was only then realized that a cash incentive equivalent to merely 3 US cents per day, and considered negligible, had actually been used to buy increased food, principally green leaves. The supplementary food purchased with this small incentive actually supplied 3 to 5 mg of available iron, together with small
amounts of protein, ascorbic acid, and vitamin A, all of which would be expected to enhance the hematological effects of the iron content of these leaves. Figure 8 shows the degree of improvement in the hematological status of the two groups.

It was possible, however, to obtain some confirmation that the effects were due to iron ingestion, and not some other factor, because repeat studies 45 days after discontinuing the iron supplementation provided evidence that we were really observing an iron supplementation effect in both groups. The anemic workers whose hematological values improved while they received the placebo were once again anemic at the end of this period. Concurrently, their Harvard Step Test scores and work output dropped and morbidity levels increased once again. By contrast, the previously anemic group that had received the iron supplement maintained their improvement in all parameters when restudied 45 days after discontinuation of the supplementation.

We showed subsequently that in Guatemala, Harvard Step Test performance returned to normal or near normal in anemic males with a period of supplementation as short as 8 days, although this was much too soon for any detectable change in hematological values. It has long been recognized that persons with moderate to severe anemia have less drive and energy and are poorer workers than those without anemia, but it had not been appreciated that such striking improvements could occur within relatively short periods of iron supplementation.

More recently, Husaini and co-workers have carried out a somewhat similar study among female tea plantation workers in the same area of Indonesia (13). Women were divided into three groups: a control group who received a placebo in pill form, a fortification group who received salt fortified with 1.5 mg of iron per gram, and a supplementation group who received iron-fortified salt plus tablets supplying 60 mg of iron per day and treatment with Combantrin to rid them of hookworm and other intestinal helminths. Weight, height, hemoglobin level, and productivity were measured before and after intervention. The result was that hemoglobin levels became normal with supplementation, but rose only slightly with fortification. When the change in mean amounts of tea leaves collected per worker per hour before and after intervention were compared, a statistically significant increase was observed only in the supplemented group.

Very similar observations have been obtained on a tea plantation in Sri Lanka, as shown in Figs. 9 (14) and 10 (15). Figure 11 (16) shows the striking increase in tea-picking productivity of anemic workers after iron supplementation compared with the lack of change in non-anemic controls. Figure 12 (16, 17) illustrates the average change in daily activity and productivity of iron-supplemented vs. control subjects. Thus, it has been possible, through both retrospective and prospective approaches, to demonstrate that the productivity of workers is related to their iron status.

The Harvard Step Test is a relatively crude indicator of work capacity, and very difficult to standardize because it requires the motivation to continue to exhaustion. It has been replaced by carefully controlled physiological studies in which a treadmill or stationary bicycle is used to estimate an individual’s maximum aerobic power ($V_{O2max}$).

Ekblom et al. (18) showed that removal of 1,200 ml of blood from normal individuals over an 8-day period reduced the duration of toleration of a given treadmill speed. A reinfusion of red cells equivalent to 800 ml of blood dramatically and promptly reversed this acute effect.  

Fig. 9. Hemoglobin status and maximum treadmill work time in Sri Lankan tea plantation workers (Gardner et al. 1977(14)). Means (±SEM) were compared using an unpaired t test between the highest Hb group and each of the lower Hb group (*p<0.05, **p<0.01, ***p<0.001).

Fig. 10. Hemoglobin and maximal work load reached in Sri Lankan tea plantation workers (Edgerton et al. (15)). HSA, severely anemic patients; HMA, moderately anemic; TMA, moderately anemic workers; TN, non-anemic workers; Pre, before transfusion; Post, after transfusion. *p<0.05; **p<0.01, ***p<0.001.

Davies and co-workers (19) studied the physiological responses to exercise of normal industrial workers compared with those suffering from moderate and severe iron deficiency anemia. They estimated that the $V_{\text{O}_2}\text{max}$ was 24% lower than normal in subjects with hemoglobin concentrations between 8 to 10 g/dl, and 35% lower in those with he-

Fig. 11. Changes in Hb and daily productivity of Sri Lankan tea pickers (tea picked) in response to oral iron treatment in subjects whose initial Hb levels were less than 9.0 g/dl (Edgerton et al., 1982(16)).

Fig. 12. Percent changes (mean ± SEM) in daily physical activity and productivity of Sri Lankan tea pickers (amount picked) in response to oral iron treatment, compared with pre-treatment control recordings in eight pairs of subjects (Edgerton et al., 1979(16, 17)).
moglobin concentrations less than 8 g/dl. Once again, it was possible to reverse these changes with iron therapy.

There are now sufficient studies showing the correlation between productivity in various tasks and the percent of $V_{O_{2}}$max that can be achieved on tests using a stationary bicycle or treadmill that adverse economic and social consequences can be inferred whenever $V_{O_{2}}$max is reduced. This has been the case in all studies investigating the effects of iron deficiency anemia. As shown in Fig. 13, from the work of Spurr et al. (20) aerobic power is significantly correlated with total body hemoglobin per unit of body weight. In subsequent studies he demonstrated a similar correlation between aerobic power and work output. Even when individuals with reduced ability to perform maximal exercise, as judged by heart rate data, manage to compensate in productivity by working harder, they are under more physiological stress than the other subjects.

Clearly, the benefits in increased productivity and work capacity from the relatively small cost of iron supplementation or fortification are potentially great, depending on the opportunities for increased work capacity to be used productively.

Cognitive Performance and Behavior

Pediatricians have often described iron-deficient children as being irritable and uninterested in their surroundings, and the apathy of adults with iron deficiency is well known. The problem has been investigated in experimental animals, and clear evidence of a positive relationship between iron status and behavior has been observed. In addition, there are now a number of clinical studies that generally include initial assessments of iron status and behavior, followed by random allocation to groups receiving either iron or placebo, and repetition of the tests after a suitable period of iron administration.

Weinberg (21) fed an iron-deficient diet to lactating female mice for 21 days as a means of producing offspring with low brain total iron, both non-heme and ferritin iron. The behavioral consequences could then be examined in these animals while holding social and environmental variables constant to a degree that is totally impossible in human studies. The response of these animals to a mildly adverse, novel environment was then observed. The animals were placed in an open area and behavior during a 3-min period was monitored for ambulation, defecation, rearing on hind legs, and standing immobile (freezing). As shown in Fig. 14, these latter two functions were sharply reduced in iron-deficient animals. Similar results were observed when iron-deficient animals were tested for re-entry to a cage after electric shock and for a number of long-term effects (21).

Recognition of the potential significance of these findings for human populations began with the
finding mentioned earlier of Pollitt et al. (2) that alterations in cognitive function in 3 to 6-year-old children with mild iron deficiency and no anemia were reversible. A battery of behavioral tests was administered to 15 iron-deficient children and 15 matched controls as well as to the formerly iron-deficient children when their iron status had returned to normal as the result of treatment. Figure 15 (22) shows the poorer performance of the iron-deficient (experimental) children compared with controls (normal iron status) on one of the tasks of oddity learning. These tasks use a card with three stimuli, two of which are identical. A child must learn that the odd figure is the correct one. After 11 to 12 weeks of iron supplementation during which time the iron status of experimental children returned to normal, the differences between the two groups disappeared. Figure 16 shows the same kind of result with a different set of cards (22).

The other kind of test employed was discrimination learning in which the subjects had to learn to discriminate between two visual stimuli. The first discrimination task included two three-dimensional objects, the second two pictures, and the third two geometric figures of different colors. The number of learning trials necessary in the iron deficiency group was significantly higher until after the iron deficiency had been corrected.

Based on these findings, a similar study was undertaken in a rural lowland population in Guatemala, where there was a high prevalence of both iron deficiency and anemia. In this study, children with a hemoglobin below 10 g/dl required more trials in the three discrimination learning tasks and in oddity-learning tasks. However, the difference between anemic and non-anemic children was not reduced by 11 to 12 weeks of iron therapy. Once again, as in the study in Cambridge, the children with iron deficiency only showed relative performance deficits on simple tasks and all differences between the two groups disappeared after the 11 to 12 weeks of iron supplementation.

In a study by Oski and Honig (23), iron-deficient, anemic infants were tested with the Bayley Scales of Infant Development, randomly given intramuscular iron or placebo treatment, and then re-tested after one week. On the Bayley Infant Behavior Record (IBR), those infants who received the iron were rated as significantly improved in reactivity and coordination after one week. A study by Lozoff and co-workers in Guatemala (24) also assessed behavioral differences between anemic and non-anemic infants based on the Bayley IBR. Table 5 shows the results on six of the IBR rating scales. Anemic infants were significantly more fearful, showed increased body tension, were less respon-
Table 5. Initial differences between anemic and non-anemic infants on the Bayley Infant Behavior Record (24).

<table>
<thead>
<tr>
<th>Behavior pattern</th>
<th>Number of infants</th>
<th>Exact probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anemic</td>
<td>Non-anemic</td>
</tr>
<tr>
<td>Withdrawn or hesitant</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Fearful</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Tense</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Unreactive to usual stimuli</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Decreased bodily activity</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Lack of persistence</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

sive to the examiner, were less reactive to ordinary stimuli, tended to be less persistent, and had a decreased amount of gross body movement. One week of oral iron treatment was not enough to improve these scores. The authors conclude that, in view of the magnitude of developmental and behavioral abnormalities in these two studies and the world-wide prevalence of iron deficiency, it is imperative to conduct additional controlled, randomized studies in other countries to determine further the effects of iron deficiency and infant behavior.

It is apparent also that cognition is adversely affected by hypoferremia in children, as shown by altered attention processes. The iron-deficient and anemic child is apparently less attentive to environmental clues that facilitate problem-solving. Once a task is learned, however, the iron-deficient child appears to process the information as well as the control child does. This is in keeping with the inferences from studies in experimental animals. It is also in accord with several other studies that suggest that the motivation to persist in intellectually challenging tasks may be lowered, attention span shortened, and overall intellectual performance diminished in iron-deficient children(2,22).

Although it is increasingly evident that iron deficiency produces behavioral changes that must be the result of alterations in brain function, the mechanisms have not been established. One theory is that altered behavior associated with iron deficiency may be related to demonstrated changes in catecholamine metabolism. This stems from the observation that monoamine oxidase (MAO) activity is decreased in iron-deficient rats. MAO is an important enzyme in the metabolism of norepinephrine, which is thought to influence behavior in man. Certainly MAO activity is decreased in iron deficiency. In infants and children, urinary excretion of norepinephrine is increased in iron deficiency, but reversed by one week of treatment. With this much evidence of important cognitive and behavioral effects of iron deficiency in humans, high priority should be given to further studies.

Iron Deficiency and Infection

One of the most important functional consequences of iron deficiency is its effect on resistance to infection in human subjects, although this is only beginning to receive systematic study. Information on the effects of iron deficiency in animals is also sparse. As shown in Table 6, the older literature contains a number of studies in dogs and cats showing increased parasitism with iron deficien-
One of the best experimental studies was done in rats by Baggs (27), who showed that morbidity (Fig. 17) and mortality in rats inoculated with Salmonella typhimurium was inversely proportional to the iron intake from the diet. The mechanisms he investigated will be discussed later.

The earliest clinical report is that of MacKay in 1928 (28). He reported that infants from poor families in London had a modest decrease in bronchitis and gastroenteritis when they received iron supplementation. The next clinical study, by Andelman and Sered in 1966 (29), included 603 infants fed a proprietary iron formula containing vitamins and 12 mg of iron per quart. Their incidence of respiratory infection was approximately half that of a group of 445 infants fed a formula with the same added vitamins but no iron.

More recently, in Alaska diarrheal and respiratory infections have been found to be more common in Eskimo and native children with iron deficiency anemia, and, as illustrated in Table 7, meningitis was often fatal in anemic children but not in those with hemoglobin levels above 10.1 g/dl (30).

Iron deficiency with or without anemia has been reported to increase the frequency of chronic mucocutaneous candidiasis (31) and recurrent herpes infection (32). In the studies of Basta and co-workers on an Indonesian rubber plantation, as mentioned earlier and as shown in Table 8, there was a decrease, with iron supplement, in the frequency of infectious disease, principally diarrheal and respiratory infections in anemic workers. The initial differences in morbidity of anemic compared with non-anemic workers completely disappeared during the 60 days of iron supplementation (33).

While not all investigators have confirmed the effects of iron deficiency on infectious disease morbidity, the experimental conditions and design vary so greatly among studies that this is not surprising. The mechanisms that reduce resistance to infection with iron deficiency have only recently begun to receive attention. In particular, a wide range of possible mechanisms has been investigated. Humoral antibody formation and leucocytosis were the classical mechanisms to be studied, usually with disappointing results. It is only with the recognition of the importance of cell-mediated immunity and related mechanisms that positive results have been obtained. The evidence for the effect of iron on these mechanisms will now be reviewed briefly.

**Iron deficiency and humoral immunity.** Formation of circulating antibodies was, until recently, considered the main defense against infection, and it can be demonstrated to be impaired by a severe deficiency of almost every nutrient. In a study in rats, Nalder and co-workers (34) found a decrease in antibody production to tetanus toxoid proportional to the severity of restriction in dietary iron. However, this has not been demonstrated in human subjects and probably does not occur with the mild to moderate iron depletion that is most characteristic of human deficiency of this nutrient. This same statement can be made about protein and vitamin deficiencies.

**Iron deficiency and leucocytes.** Iron deficiency consistently interferes with the function of leucocytes through cellular mechanisms that require iron-containing enzymes. Most striking is the reduction in myeloperoxidase necessary for the killing

<table>
<thead>
<tr>
<th>Hemoglobin (g per 100 ml)</th>
<th>Fatal</th>
<th>Non-fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>&lt;7.0</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>7.1–10.0</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>&gt;10.1</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

(Fortune, 1966 (30))

Table 8. Morbidity before and after 100 mg FeSO₄ daily for 60 days (% prevalence 4 weeks preceding study and last 4 weeks of intervention).

<table>
<thead>
<tr>
<th>58 Anemic</th>
<th>I</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Influenza&quot;</td>
<td>15.5%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Enteritis</td>
<td>6.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Mean score</td>
<td>1.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Fig. 18. Of bacteria. In the studies of Baggs et al. described earlier, an increased susceptibility of iron-deficient rats to Salmonella typhimurium was demonstrated, as shown in Fig. 17. Figure 18 shows the reduced ability of macrophages from iron-deficient rats to kill Salmonella in the wall of the gastrointestinal tract. This can be at least partially explained by a reduction in myeloperoxidase-containing granulocytes in the intestinal wall.

In human subjects, iron has been shown to cause a defect in microbicidal capacity, as judged by the in vitro NBT dye (nitroblue tetrazolium) test (32), and impaired formation of hydroxy radicals due to decreased iron saturation of lactoferrin in neutrophils, as illustrated in Fig. 19. These effects are promptly reversed by iron therapy. Studies are required, however, of the effects of iron deficiency on phagocytic killing power in human populations with mild to moderate degrees of iron deficiency. Those currently under way in Indonesia and Egypt with UNU support are designed to provide this information. Preliminary results from both these studies indicate that there is impairment with even mild iron deficiency, but the iron supplementation has only just started.

Cell-mediated immunity. Rats deprived of iron show a mild atrophy of lymphoid tissues and a more marked depletion of lymphocytes (35). The number of splenic antibody-forming cells is also reduced. In iron-deficient mice, killer T cell activity was found

Iron deficiency in human populations to be reduced (35).

Bhaskaram and Reddy (36) found a significant reduction in the percentage of circulating T cells in nine iron-deficient children (42 versus 65% in controls) and in proliferative response to phytohemagglutinin (PHA) (4.5 versus 27.3). After iron supplementation, T cells rose to 52% by the fourth week, but the PHA proliferative response was still depressed (SI = 5.0).

Srikantia and co-workers (37) divided 88 children into four groups according to hemoglobin levels: severe and moderate iron deficiency (<8.0, 8.1 to 10.0 g/dl), mild deficiency (hgb 10.1 to 12.0 g/dl), and normal controls (>12 g/dl). In severely and moderately anemic groups, there was a significant depression in E-rosette formation and response to PHA by peripheral lymphocytes compared to results in mildly anemic or control groups of children. In severely iron-deficient children E-rosettes were reduced from 58.7 to 37.9%, and PHA SI decreased from 19.4 to 5.9. In moderately deficient children 47.3% of lymphocytes formed E-rosettes, and the SI was 13.3. Results in those with mild deficiency did not differ from normal control results.

Percent transferrin saturation was also measured in these children with low (<10.0 g/dl) and high (>10 g/dl) hemoglobin levels. In the low hemoglobin group, those with transferrin saturation greater than 15% had 34% E-rosetting cells and PHS SI of 3.6, and children with transferrin saturation below 15% had 44% T cells in peripheral blood and SI of 10.4. Transferrin saturation is apparently a better indicator of depressed T lymphocyte functions than is degree of anemia.

Iron-deficient children have a decreased percentage of T lymphocytes that is corrected by 4-weeks of iron supplementation (32, 38, 39). A diminished production of macrophage inhibition factors by the lymphocytes of patients with iron deficiency anemia has been reported (40). In general, T cells from which the various kinds of lymphocytes are derived are reduced in iron-deficient animals and humans (32), and in the electron microscope studies of lymphocytes from iron-deficient patients, 40% were found to have various changes in their mitochondria (41). Authors from around the world have observed a decreased lymphocyte production in response to mitogens, and lower values for lymphocyte ribonucleotide reductase have also been demonstrated. All of these findings are reversed by iron supplementation.

Delayed cutaneous hypersensitivity. When antigens are injected intradermally into well-nourished individuals sensitized to them, a reddening and swelling develop within 2 days. The lesion varies in size with the intensity of the stimulus. It is well established that this response is decreased or absent in severe protein deficiency, where serum transferrin serves as an indication of protein nutritional status. Delayed cutaneous hypersensitivity to a number of ubiquitous antigens has also been described in iron-deficient children in India (36) and Kenya (42).

Effect of iron excess

Bacteria require adequate quantities of iron for their replication. Some bacteria have siderophores that chelate iron and increase its availability to the bacteria. During an infectious process in animals or humans, the availability of iron to microorganisms is markedly reduced by the rapid sequestration of iron in the reticuloendothelial system and by sizable amounts of unsaturated transferrin and lactoferrin molecules. These have sufficiently strong binding affinities to withhold iron from bacterial siderophores. Additional lactoferrin is released by phagocytizing white blood cells in areas of localized inflammatory response, and this helps to restrain local bacterial growth.

Low concentrations of transferrin associated with protein deficiency remove some of this protective effect, contributing to the susceptibility to infections of malnourished animals or humans. Since both humoral and cell-mediated immunity are impaired with the severe protein deficiency relative to calories that results in kwashiorkor, it is not surprising that administration of iron to children with kwashiorkor before protein repletion has restored immune mechanisms has been reported to increase fatalities from overwhelming bacterial sepsis (43).

Exacerbation of malaria after iron therapy of patients with iron deficiency anemia has been noted in both Nigeria (44) and Somalia (45). In starved Sahelian drought patients whose iron concentrations rose rapidly to saturation after a few days of
re-feeding, parasitism increased from less than 5% to greater than 50%, and the onset of severe clinical malaria, often of the cerebral variety, was observed. As shown in Fig. 17, discussed earlier, Baggs and Miller (27) found that an iron-free diet protected rats from morbidity and mortality after a dose of Salmonella typhimurium.

It would be a serious error, however, to assume that, because the multiplication of infectious agents is impaired by severe deficiencies induced in experimental animals, malnutrition of any kind in human populations is desirable. For the great majority of common infections, the interference with host resistance mechanisms of even moderate nutritional deficiency is far more consequential. In general, resistance to infection is reduced by the common degrees of human malnutrition without their being severe enough to affect the infectious agent.

Thermoregulation

Abnormalities in thermoregulation due to iron deficiency were first described in experimental animals by Dillman and Finch et al. (46, 47). When compared to control animals, iron-deficient rats exposed for 6 h to a temperature of 4°C showed a greater decrease in body temperature, a higher plasma norepinephrine level, and a retarded conversion of the thyroid metabolite T4 to T3. This was not due to changes in body insulation because hair thickness was unaltered, and differences persisted after removal of hair, and cutaneous vasoconstriction was intact. However, the oxygen consumption of iron-deficient animals at 4°C was reduced (39 ± 3 ml/kg/min compared to 63 ± 3 in control animals). T3 values of iron-deficient animals in the cold were 48 ± 6.8 ng/dl as compared to 72 ± 5.6 in control animals. Treatment of iron-deficient animals with iron normalized responses at 4°C within 6 days. The authors proposed that an impairment of conversion of T4 to T3 with iron deficiency is responsible for the hypothermia observed in iron-deficient animals.

Figure 20 shows the lowering of body temperature by d-amphetamine-induced hypothermia in iron-deficient as compared with control animals (48). Figure 21 shows the lower rectal temperature of iron-deficient rats exposed to cold compared with control animals. Iron supplementation for as short a period as 6 days abolished the difference between experimental and control animals. These changes are inversely reflected in the urinary norepinephrine excretion (49).

I have long been fascinated by the phenomenon of non-shivering thermogenesis, the mechanism

whereby individuals can increase their internal heat production when exposed to cold. While this is in part an adaptive phenomenon in the sense that it improves over a period of weeks of periodic exposure to cold, it is a characteristic of normal human metabolism. It is a common observation that periods of "cold" weather that would not be uncomfortable for persons in industrialized temperate countries can cause great suffering and even reports of death among the poor in countries such as those of the Asian subcontinent. To my knowledge, there have been no systematic studies of the possible role of iron deficiency or other nutritional deficiencies in the inability of developing country populations to withstand even moderately lowered environmental temperatures.

However, studies have been carried out in Caracas, Venezuela with human subjects relaxing in a circulation tank under conditions in which blood pressure, body temperature, and oxygen consumption could be monitored and periodic blood samples obtained. When the temperature was lowered from 36°C to 28°C, the five subjects with severe iron deficiency were unable to maintain body temperature. However, there was less of an increase in oxygen consumption over a 60-min period of cooling in both those with mild and severe iron deficiency anemia. Norepinephrine was elevated in the five subjects with iron deficiency but no anemia, and in those with iron deficiency and anemia as compared with normal subjects.

Differences were found in the levels of epinephrine, dopamine, T3 and T4 among the various groups of subjects. When the iron-deficient subjects were treated with 60 mg of iron three times a day for 7 days, oxygen consumption returned to normal, even though the hemoglobin, transferrin, and ferritin did not have time to change significantly. When the subjects were given 200 mg of iron parenterally, interferon and norepinephrine levels returned to normal. While the results are suggestive, it is clear that the issue of iron deficiency and temperature regulation merits additional detailed and systematic investigation in human subjects.

In summary, there are many studies demonstrating the world-wide prevalence of iron deficiency anemia and a number demonstrating recovery with supplementation or fortification of staple foods with iron. However, the functional significance, not only of iron deficiency anemia, but also of iron deficiency not severe enough to cause anemia is only just beginning to be appreciated. I have brought together in this paper the still fragmentary evidence that, in human populations, iron deficiency significantly impairs function in a way that must certainly impinge on economic development and social welfare.

REFERENCES


42) (ref. to Fe-deficient children in Kenya and delayed cutaneous hypersensitivity to be supplied).


