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# Functional Significance of Iron Deficiency

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## KEYNOTE ADDRESS

# FUNCTIONAL SIGNIFICANCE OF IRON DEFICIENCY

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### Introduction

Iron deficiency is the most widespread nutritional problem in the world today and, unlike the classical deficiency diseases, also still affects substantial numbers of persons in the United States and other industrialized countries. A recent report from India gives an anemia prevalence of 60-80% for pregnant women in different regions of India (1). If iron deficiency rather than anemia is the criterion, it has been suggested that one-third of premenopausal women in the United States fall into this category, with minority groups more heavily affected.

Using data from NHANES II for 1976-80, the Life Sciences Research Office (2) reported high frequencies of impaired iron status in U.S. preschool children and premenopausal women, particularly among those whose incomes are below the poverty level. The report documents an overall 7.2 per cent prevalence of actual anemia in women 15 to 44 years of age, but with the highest burden in minority and poverty groups. For example, the 1976-80 NHANES II figure for the percentage of persons with two or three abnormal iron status indicators was 11.7% for white and 31.3% for black adolescents 15 to 19 years of age.

There are several overlapping stages of iron status ranging from iron excess to iron deficiency anemia. Anemia is generally diagnosed on the basis of the WHO standards for various age and sex groups (3). For determining iron status the criteria shown in Figure 1 have been proposed for adults, with small adjustments for younger age groups (2). In the first stage of iron deficiency,

plasma transferrin is increased and ferritin markedly decreased. Erythropoiesis is affected when, in addition, plasma iron and transferrin saturation are decreased and iron protoporphyrin elevated.

In iron deficiency anemia these values are further altered, and the erythrocytes are seen to be microcytic and hypochromic. Intestinal iron absorption increases progressively with iron depletion. It is now clear that earlier biochemical changes and not the reduction in circulating hemoglobin are the primary factors responsible for the alterations in muscle and central nervous system function in anemic subjects. With iron overload, plasma iron and ferritin levels as well as iron deposits in various tissues are greatly increased and transferrin iron-binding capacity is elevated.

While approximately 73% of the body's iron is normally incorporated into hemoglobin and 12% in the storage complexes ferritin and hemosiderin, a very important 15% is incorporated into a variety of other iron-containing compounds, some of them enzymes of vital importance. The heme compounds include myoglobin, cytochromes, catalases and peroxidases. The non-heme compounds include NADH and succinic dehydrogenases; xanthine, aldehyde and alphasglycerophosphate oxidases; phenylalanine hydroxylase; and ribonucleotide reductase. Alphasglycerophosphate oxidase, for example, shuttles electrons across the mitochondrial membrane. Also important are the iron-dependent enzymes: lipid peroxidase, proline and lysine hydroxylase and a number of others.

While there can still be considerable discussion of the best cutoff points for maximum sensitivity and specificity of diagnosis in various circumstances, the important issue is their application to the identification of vulnerable groups and the functional significance of these categories. Although the papers to follow in this symposium will cover each of the topics in more detail, I would like to give an overview of what is known of the impact of these stages of iron status on various functions.

### **Human reproduction**

In normal men the combined daily loss of iron through the urine, skin and feces is only about 1 mg. The iron requirements of women under various circumstances are analyzed in detail in an excellent INACG publication (4). Because of their smaller body size, losses in women from these sources is less, perhaps 0.7-0.8 mg daily, but median menstrual losses averaged over a month add the equivalent of another 0.4 - 0.5 daily. However, these menstrual losses are very asymmetrically distributed, with 10% of normal women experiencing losses three times the median. In some women the use of conventional intrauterine devices for contraception leads to increased vaginal blood loss. Even without other adverse factors these women are at obvious risk. While menstruation temporarily ceases during pregnancy, the overall iron cost to the mother is greater, around 5 mg. daily, during the second and third trimesters. To this must be added the iron lost in blood at delivery and in lochia later in the puerperium, around 150 mg; but once again, there is great individual variation.

For underprivileged populations, poor iron availability and often pathological iron losses associated with parasites greatly increase the prevalence of iron deficiency in women who, already in borderline status, are the most seriously affected. Under these circumstances the physical demands on women for procuring food and other economic activities as well as food preparation and family and home maintenance are great,

and iron deficiency reduces their capacity to meet these demands.

In addition to the consequences of iron deficiency affecting all persons, to be discussed later, there are additional adverse consequences of iron deficiency in childbearing women. Maternal mortality, prenatal and perinatal infant loss, and prematurity are significantly increased. If the mother is iron deficient during pregnancy, her infant is born with poor iron reserves and is at greater risk of morbidity and mortality during infancy (4). Low-birth-weight infants exhaust their iron stores at an earlier age and require more iron than supplied by breast milk at an earlier age than infants of normal birthweight (5, 6).

### **Child Growth**

In three separate studies in Indonesia, iron supplementation resulted in significantly increased growth of children (7, 8) compared with that of children receiving placebo. Since no other study using iron supplementation appears to have included growth measurement, there is a need to confirm this finding in other populations. If confirmed, the result could be due either to a direct effect of iron itself or to increased food intake because appetite is enhanced in persons whose iron deficiency is reversed.

### **Physical capacity**

Well before studies with human subjects, the effect of iron deficiency on physical performance was explored in experimental animals. Edgerton et al. (9) showed a linear relationship between hemoglobin and change in spontaneous activity in rats relative to control rats (Figure 2). A similar relationship was found in rats for running time to exhaustion. Figure 3 from Finch et al. (10) shows the poor treadmill performance of rats on an iron deficient diet for 3 and 4 weeks compared with groups receiving adequate iron, and a progressive improvement in iron deficient rats with supplementation. Other workers (11,12,13) report similar results.

These observations were replicated later in concurrent studies of human subjects in Guatemala and Indonesia. Figure 4, from Viteri et al. (14), shows a linear correspondence between hemoglobin status and Harvard step test (HST) results. In subjects this performance improved with iron supplementation. In Indonesia Basta et al. (15) found similar differences in HST scores between anemic and non anemic road construction workers and rubber tappers who had improved performance when they were given iron for 30 days, before significant improvement in hemoglobin status.

Among male tea pickers in Sri Lanka the results were similar (16). In both Sri Lanka and Kenya treadmill was proportional to plasma hemoglobin. Spurr et al. (17) also found linear correlations between hemoglobin status, aerobic power and other measures of physical capacity in Colombian laborers.

#### Work performance and productivity

The question remains as to whether these observed differences in physical capacity affect productivity. Basta et al. (15) subsequently showed a strong correlation between hemoglobin status, HST performance and the take-home pay of Indonesian rubber tappers (Figure 5). Tappers given iron supplementation for 60 days increased their take-home pay by more than 30%. Among the weeders who were not paid on an incentive basis less area was weeded by those who were anemic, and their output also increased with supplementation.

In a subsequent study in Indonesia by Husaini et al. (18), the mean amount of tea leaves collected per hour was significantly less for anemic women; work output increased by 24% after four months of iron supplementation. Similar results were obtained in a larger follow-up study sponsored by UNU on four other tea plantations in the same area. Figure 6 shows that the daily productivity of the anemic male tea pickers in Sri Lanka increased more than 20% after iron supplementation for 1 month (19,20). An

increase in agricultural productivity of Indian women (21) given iron supplementation has been reported. Productivity also increased with the iron supplementation of anemic male agricultural workers in Colombia (17).

#### Morbidity from infection

In experimental animals, iron deficiency has been associated with the severity of hookworm infection in rats (22), cats and dogs (23), and with increased morbidity and mortality in rats experimentally infected with salmonella (24).

Poorly nourished infants in London were reported in 1928 to have less bronchitis and gastroenteritis when they received iron supplementation (25). However, considering the widespread occurrence of iron deficiency, subsequent observations on the effect of iron deficiency on morbidity from infections are relatively meager. The first modern controlled observation that I could identify came nearly 40 years later and demonstrated that infants receiving a proprietary formula with vitamins and iron had approximately half the respiratory infections of infants given the same formula unsupplemented (26).

Iron deficiency in Alaskan native children has been reported to be associated with increased diarrheal and respiratory disease (27), and meningitis was observed to be fatal only in anemic children (28). The study of Basta et al (15) in Indonesia, mentioned earlier, found that the greater morbidity from infection among the anemic rubber tappers decreased after iron supplementation. In both the Egyptian (29) and Indonesian (18) field studies, a decrease in diarrheal and respiratory infections was observed in the groups receiving iron supplementation.

There is evidence from Guatemala that vitamin A deficiency exacerbates iron deficiency (30), and from both Guatemala and Indonesia (31), that supplementation of poorly nourished child populations with vitamin A results in improved iron nutriture. The implications of this interaction have not been explored. However, the administration

of vitamin A in periodic massive doses in Indonesia (32), and similar programs in progress in a number of other countries, have shown significant reductions in morbidity and mortality from infections (33). Some or all of this may be mediated through the effect of vitamin A on their iron status.

### Deficiency and immunity

Information on mechanisms whereby iron deficiency results in increased morbidity is also relatively limited, but a number of antimicrobial systems (within the neutrophil) are adversely affected by iron deficiency. In the study previously referred to, of experimental salmonellosis in rats, by Baggs and Miller (24), both viable intracellular and extracellular bacteria were observed in greater numbers in the macrophages and in the intestinal wall of the iron-deficient rats compared with iron replete animals. This is paralleled by the concentrations in the intestinal wall of the iron-containing enzyme myeloperoxidase that mediates the iodination of proteins and the formation of hydrogen peroxide to kill microorganisms within the cell (Figure 7).

Superoxide produced by the action of the enzyme superoxide dismutase is also involved in the respiratory burst that is part of the mechanism for killing organisms ingested by leukocytes (34). Chandra et al. (35) have demonstrated in Indian children that the mitogenic response of the lymphocytes, the capacity for respiratory bursts necessary for killing ingested organisms, and the number of intracellular bacteria in lymphocytes exposed in culture are related to transferrin saturation (Figure 7). The relationship between hemoglobin status and *in vitro* bactericidal activity is shown more clearly in Figure 8 (35).

There is extensive evidence from India (36, 37, 38) for a direct relationship between iron status and plasma T-lymphocyte concentrations. Impaired delayed cutaneous hypersensitivity to a number of ubiquitous antigens has also been described in iron-deficient children in India (36) and Kenya. Ad-

ditional evidence for the effects of iron deficiency on immunity has been reviewed by Keusch (39).

### Cognitive performance and behavior

Recently, more attention has been paid to the relationship between iron status and cognitive performance than to any other functional consequence of iron deficiency. While there were a number of relevant earlier studies in experimental animals (40-47), in 1973, Webb and Oski (48) reported improvement in the cognitive performance of iron-supplemented adolescents, but since there was no control group a practice effect was suspected. In 1978, Oski and Honig showed an improvement in the Bailey scores of anemic infants given iron supplementation compared to those achieved by a placebo group (49).

I believe that credit for the first demonstration of an adverse effect of iron deficiency even without anemia belongs to Pollitt and coworkers (50, 51). They found that, on a battery of cognitive and behavioral tests, mildly iron deficient 3-6 year old children in Cambridge, Massachusetts had lower scores than those with normal iron status, but the low scores returned to normal after children were given 11-12 weeks of supplementary oral iron. Pollitt then repeated these studies with preschool children in Egypt and Indonesia (52). Figure 9, based on the Cambridge data, typifies the results in Cambridge and Indonesia, but with the moderate to severe anemia of children in Guatemala and Egypt, there was no significant cognitive test improvement in anemic children within the two to three month period of supplementation, even though their hematological deficit was corrected.

Concurrently with these studies, Lozoff in Guatemala (53) and subsequently in Costa Rica (54), Stekel (55) and later Walter (56, 57, 58) in Chile, tested anemic and control infants using the Bailey scale. Table 1 typifies the findings of impaired performance in the anemic groups in these studies. However, except in the Stekel (55) and Oski and

Honig studies (49), most of the children failed to respond to even three months of supplementation, raising the alarming possibility that the effects of anemia are lasting.

Two studies by Soemantri et al., in Indonesian school children (7, 8) not only documented poor performance by those initially iron-deficient, but they also observed substantial recovery after 12 weeks of iron supplementation. The results in four studies of school-age children in India were similar (59). However, a double-blind study of 1358 children 9 - 11 years old by Pollitt et al. (60) in Thailand found a positive association between iron status and performance on the Raven Progressive Matrices used to measure IQ, a Thai language and a math test. It is noteworthy that children who were iron-depleted without anemia obtained significantly lower scores in Thai language than did iron-replete children. While the IQ and math scores were also lower in the iron-depleted, the difference was not statistically significant. However, no significant improvement was observed following 100 mg of iron as ferrous sulfate per day for 14 weeks. The overall results of these various studies suggest that iron deficiency is educationally disadvantageous regardless of ethnicity and physical and social environment.

It is evident that key iron-containing compounds in the brain respond to iron deficiency even when the deficiency is not sufficiently severe to affect hematopoiesis. Recent work from Israel with iron-deficient rats (61, 62) suggests that selective diminution of central dopamine neurotransmitters may be a key mechanism. It is postulated that interference with iron metabolism at an early age could result in irreversible damage to developing dopamine neurons, with consequences evident in later life.

### Temperature regulation

There are a number of studies reporting that iron-deficient rats exposed to low environmental temperatures are unable to maintain their body temperatures (63, 64, 65). There is an associated increase in plasma

norepinephrine and a retarded conversion of the thyroid metabolite T4 to T3. Figure 10 is an example of the findings in these animal studies. These findings have been replicated with volunteer human subjects in Caracas, Venezuela, by exposing them for one hour successively to water baths of 36°C and 28°C (M. Layrisse, personal communication).

### Overload and infection

It is important for this workshop to discuss the consequences of excessive dietary iron as well as iron deficiency for two reasons. First, there are circumstances in which the administration of parenteral or large oral doses of iron can lead to overwhelming infections. Second, failure to understand the special circumstances under which this occurs can interfere with needed programs of iron supplementation and fortification for populations at risk of iron deficiency.

It is not only the host that needs iron for the biochemical functions mentioned in the introduction, but also the infectious agent (66). Without it, replication is inhibited. In fact, withholding iron from the infectious agent appears to be an important mechanism of resistance to infections (67, 68). Conalbumin and lactoferrin have stronger iron binding properties than most bacterial siderophores and are normally highly unsaturated and function as iron-withholding rather than iron-transport agents.

Lactoferrin, known to be released upon degranulation of leukocytes in aseptic areas, is a major component of human milk and resists proteolytic destruction in the gastrointestinal tract. It is not difficult to demonstrate in vitro the protective effect of lactoferrin (69). In the iron-deficient host with reduced cell mediated immunity and leukocyte function, lack of available iron for agent replication is protective. Baggs and Miller (24) found that in rats exposed to a standard dose of Salmonella, a diet lacking in iron is almost as protective as one meeting iron needs.

Murray and Murray have described the

exacerbation of malaria with a high case fatality rate in Somalia refugees given therapeutic doses of iron (70, 71). Parenteral iron given to children with kwashiorkor has also been associated with mortality from overwhelming infection (72, 73). However, in our supplementation studies in Egypt (29) and Indonesia (31), morbidity from diarrheal and respiratory disease decreased promptly with iron supplementation. The iron supplement promoted recovery of immune function without providing enough iron to increase the severity of existing or subsequent infections.

#### **Iron Status and cancer**

The final topic to be considered is the possibility of a relationship between high iron intakes and the risk of some kinds of cancer (74-77). These reports have presented evidence that increased body iron stores, as judged from serum ferritin levels, are associated with an increased cancer risk. Although these studies are preliminary and inconclusive, they provide an additional reason for avoiding iron excess as well as iron deficiency. The mechanisms involved may be comparable to those seen in the effect of iron overload on infections, i.e., adverse effects on the immune system and a reduction in capacity to lower rapidly replicating cells.

#### **Summary**

In summary, iron deficiency has been shown to affect adversely the physical capacity and work performance of adolescents and adults, the cognitive performance and behavior of infants, preschool and school children, immune status and morbidity from infections of all age groups, and the maintenance of body temperature in adults exposed to a cool environment. In general, these effects are corrected by iron supplementation, but in the case of children with moderate to severe iron deficiency anemia, the effects on cognition may not be reversible.

In addition to a genetic defect resulting in excessive iron absorption and overload leading to serious liver pathology, excessive dietary iron may produce the same results in exceptional circumstances. In children and adults who are immunologically compromised by severe malnutrition and heavily exposed to infection, the administration of parenteral iron or a large dose of oral iron may result in overwhelming infection. Excessive iron intakes may also favor some forms of cancer. However, the amount of iron provided in programs of fortification of staple foods and in routine prenatal iron supplementation has been repeatedly demonstrated to improve reproductive performance, enhance resistance to infections, and increase work capacity and productivity without observable risk.

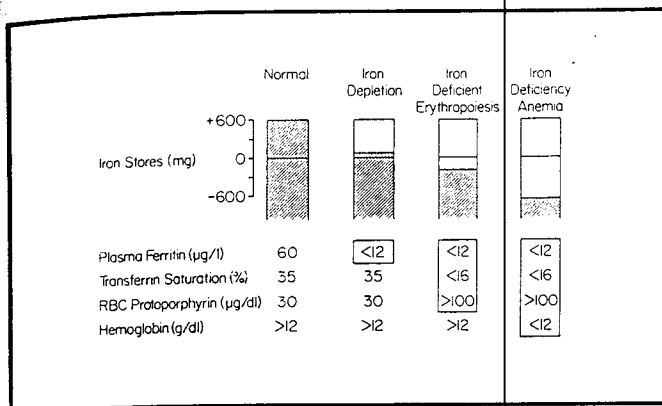


Figure 1. Measurements of iron status in relationship to body iron stores (mg). Negative iron stores indicate the amount of iron that must be replaced in circulating red cells before iron reserves can re-accumulate. Ref. 3.

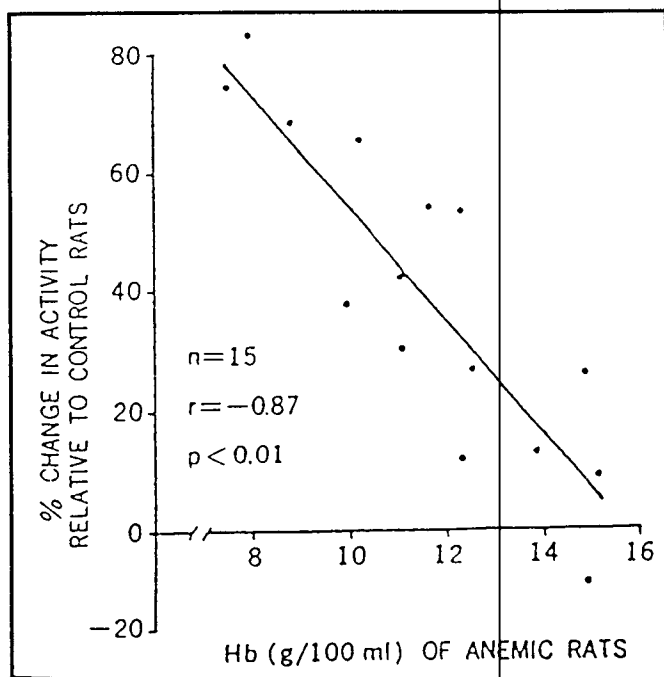


Figure 2. The relationship between Hb and percent differences in voluntary activity between anemic and control groups is shown. Percent change in activity =  $-9.56(\text{Hb}) + 149.59$ . Ref. 9.

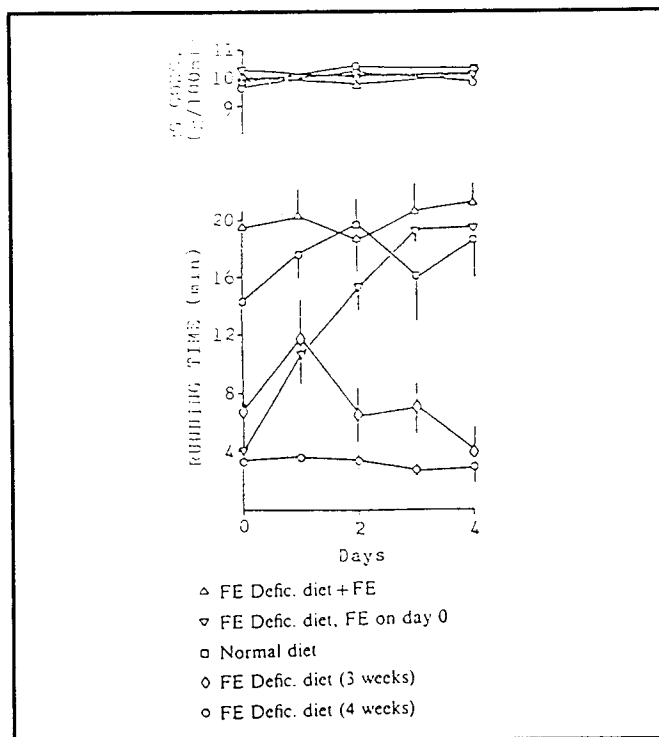


Figure 3. Work performance at 10g/100ml hemoglobin by normal and iron-deficient animals (Finch *et al.*, 1976 [7]). Ref. 10.

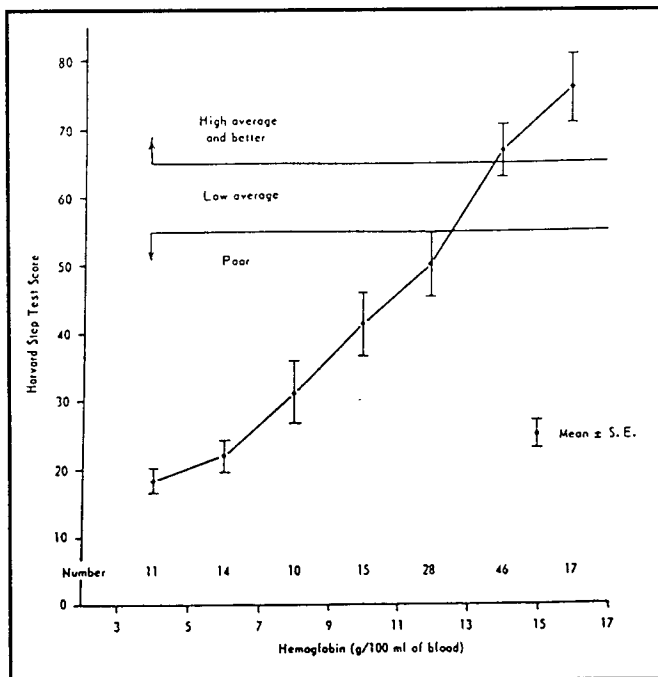


Figure 4. Physical fitness in relation to hemoglobin concentration in Guatemalan agricultural workers. Ref. 14.

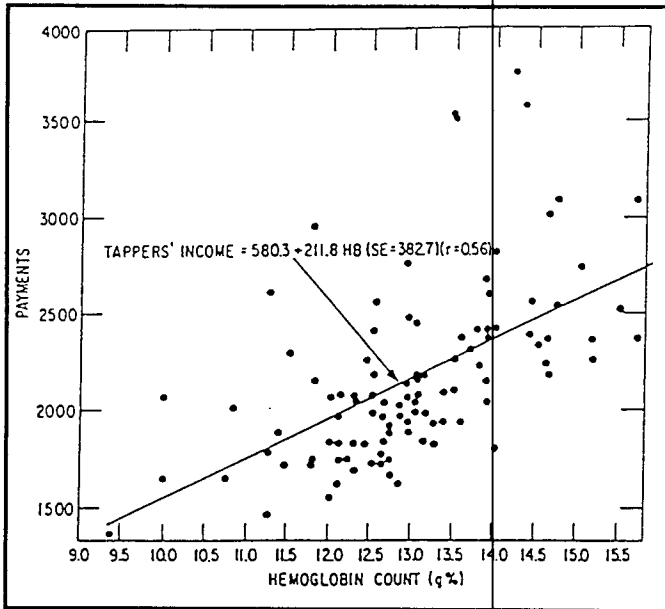


Figure 5. Hemoglobin versus Tappers' income (preintervention program). Ref. 15.

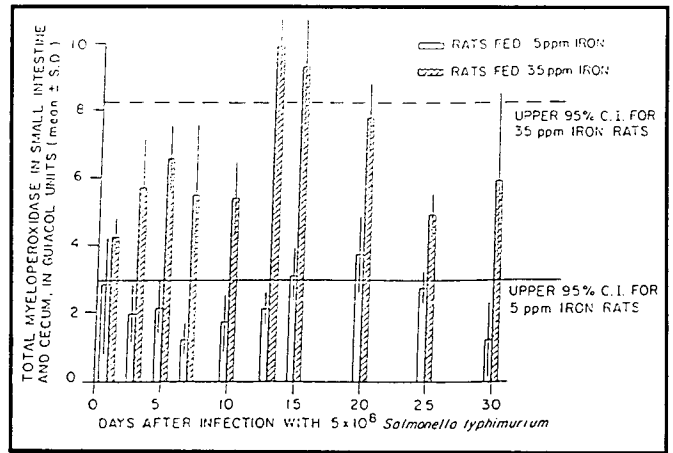


Figure 7. Ref. 24.

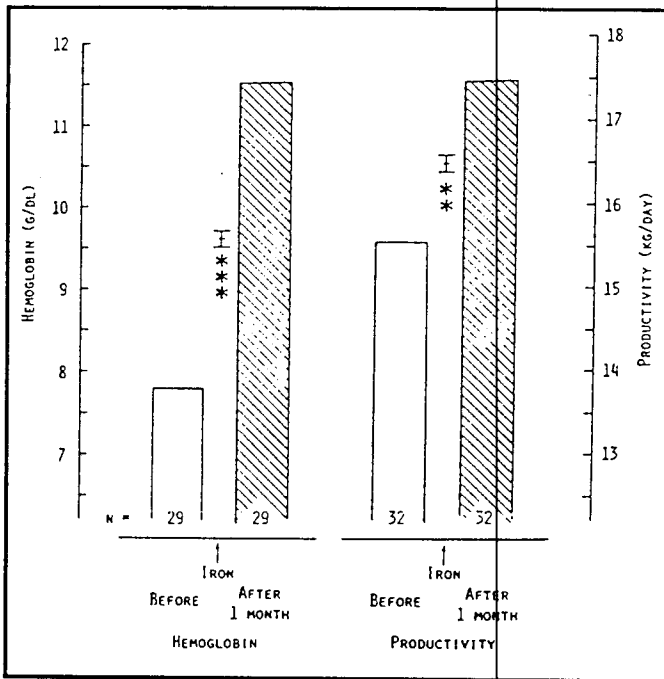


Figure 6. Changes in Hb and daily productivity (tea plucked) in response to oral iron treatment in subjects whose initial Hb levels were less than 9.0 g/dl.  $**p < 0.01$ ,  $***p < 0.001$ , and vertical bars (mean  $\pm$  SEMD) were obtained from paired *t*-tests between the values before and 1 month after iron treatment. *N* represents the number of subjects. Ref. 19-20.

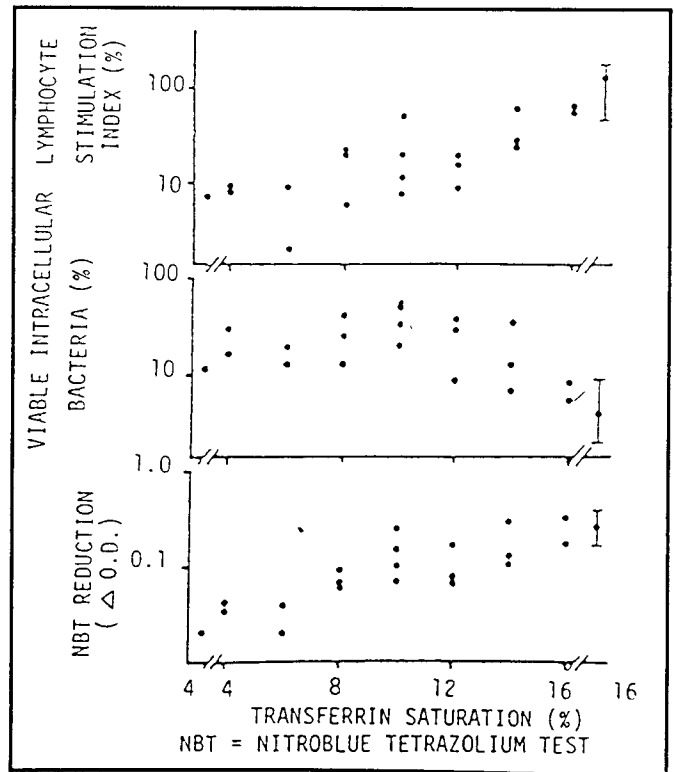


Figure 8. Correlation between depressed *in vitro* response and transferrin unsaturation in children (32). NBT, nitroblue tetrazolium test. Ref. 35.

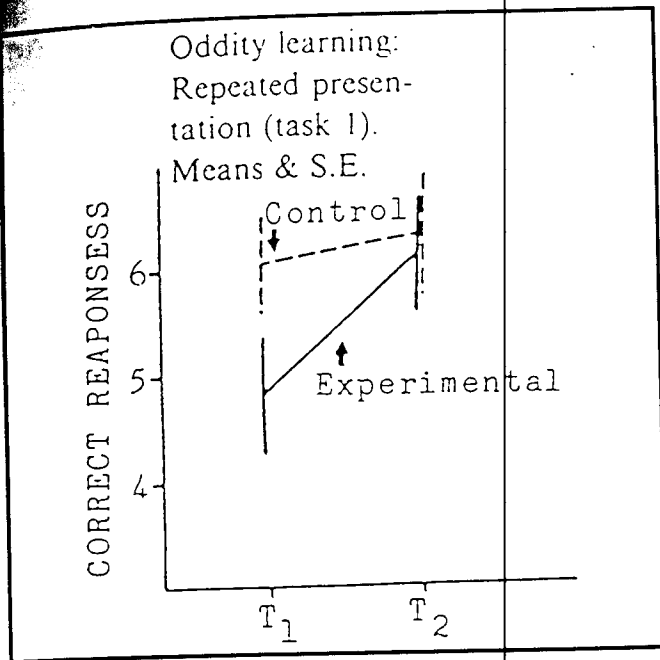


Figure 9. Performance of control and experimental groups of children on oddity learning tasks before (T<sub>1</sub>) and after (T<sub>2</sub>) administration of oral iron. Ref. 50.

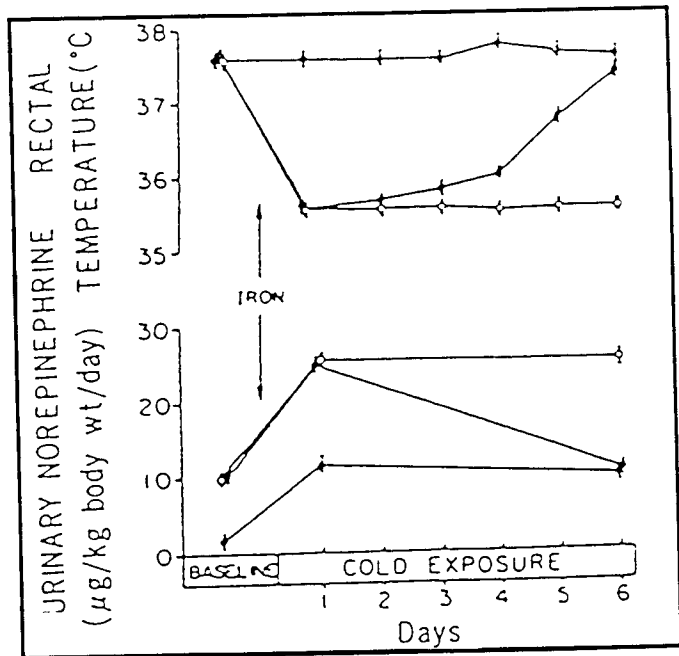


Figure 10. Effects of iron treatment on temperature regulation and urinary catecholamines in iron-deficient and control rats (Dillman *et al.*, 1982 [49]). Iron deficient rats, ○; iron deficient rats treated with iron. ○; control rats. ○.

Table 1.

Behavior pattern	Number of infants		Exact probability
	Anemic	Non-anemic	
Withdrawn or hesitant	6	2	0.05
Fearful	7	2	0.02
Tense	7	1	0.01
Unreactive to usual stimuli	7	3	0.05
Decreased bodily activity	7	4	0.07
Lack of persistence	8	5	0.10

Ref. 52

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