

Iron and Infection

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The interaction between host and infectious agent is a complex phenomenon, and no theory or experimental model has encompassed that complexity. The central focus of scientific inquiry should be to identify the basic processes and factors of both the human immune response and infectious agent virulence. When reviewing the literature on the relationship of iron deficiency to infection, one encounters conflicting data and divergent results. Some investigators favor the contention that mild iron deficiency is "good" for immunity, while others contend that any iron deficit is not good for immunity.

To examine this controversy, we will address (a) the relationship of iron to the immune response *in vitro*; (b) the evidence that administration of iron may promote infection; (c) evidence that iron may protect against infection; (d) the effect of parenteral iron therapy; and (e) the effect of iron-fortified foods on infection during infancy.

IMMUNE RESPONSE *IN VITRO*

Two immune system abnormalities associated with iron deficiency have been documented in humans: an impaired response of T-lymphocytes to mitogens and a decreased bactericidal activity of neutrophils. The DNA synthesis of T-lymphocytes in response to stimulants or mitogens results in "blastic transformation" and the production of lymphokines that are important for immune regulation. A continuous supply of iron is required for the activity of mammalian ribonucleotide reductase (1), an obligatory step in DNA synthesis (2).

Joynson et al. (3) described an impairment in lymphocyte transformation and production of migration inhibition factor after *Candida* and purified protein derivative (PPD) antigen stimulation in 12 subjects with iron deficiency anemia. Both the proportion and absolute number of T-lymphocytes were reduced in iron deficiency anemia. Lymphocyte proliferation and response

to phytohemagglutinin (PHA) and Con A antigens were impaired in iron deficiency without anemia, and there was a significant correlation between the stimulation index and transferrin saturation (4-6). In a recent study of 10 iron-deficient children aged 12 to 30 months, the mean stimulation index for *Candida* antigen increased from 6.8% to 17.9%, and for tetanus antigen from 19.5% to 31.7%, following iron therapy (7).

A defect in neutrophil function in iron-deficient patients could also predispose them to bacterial infection. Although it is generally agreed that phagocytosis, or ingestion of bacteria, is normal in the presence of iron deficiency (8-10), the capacity for killing certain types of bacteria once they have been ingested is impaired (11-13). At least two or three iron-dependent steps are involved in intracellular bacterial killing. A sharp increase in oxygen consumption or the "respiratory burst" (14) results from the activation of NADPH oxidase (presumably an iron-sulfur enzyme), which produces O_2^- and H_2O_2 . The heme protein cytochrome b is also associated with the "respiratory burst" in a way yet to be clarified. $^{\cdot}O_i$ and $O_2^{\cdot-}$ are used to produce oxidized halogens and OH-radicals, which are effective in bacterial killing. The heme-iron enzyme myeloperoxidase mediates the halogenation of bacterial protein using H_2O_2 . The production of OH-radicals is catalyzed by the iron present in leukocyte lactoferrin by way of the Haber-Weiss reaction (15).

Neutrophil function defects have been demonstrated *in vitro* for humans by Chandra. Walter et al. (16) have studied neutrophil function in 10 iron-deficient but otherwise healthy infants 6 to 23 months of age. Neutrophil function and iron status were assessed at 0, 3 to 5, 15, 30, and 90 days after oral iron therapy had been initiated. Although phagocytosis was unaffected, bactericidal activity was profoundly impaired before therapy, improved partially at 3 to 5 days, and was completely corrected at 15 days. The timing of recovery suggested that iron had no effect upon circulating neutrophils but was required for neutrophil development in the bone marrow. This finding is in accordance with the rate of recovery of myeloperoxidase activity in iron-deficient rats. In these iron-deficient rats, however, the "oxidative burst" was maintained, allowing other bacterial killing mechanisms to continue (17). This finding in the animal model may explain why no overt clinical signs (respiratory, gastrointestinal, or cutaneous) could be identified in this group of children either before they were studied or during the subsequent 15 days of close clinical and laboratory follow-up, in spite of profound *in vitro* immune defects. The clinical significance of these laboratory findings of immune function defects in moderately to severely iron-deficient infants is questionable.

The preceding studies provide convincing evidence of an unfavorable effect of iron deficiency on human T-cell and phagocyte function *in vitro*. In addition, bacteria require iron for growth, and increased iron availability enhances bacterial virulence. In fact, iron is avidly bound by bacterial iron

transport cofactors called siderophores. The iron-binding affinity of siderophores is comparable to that of transferrin. Several *in vitro* experiments have shown that the addition of unsaturated transferrin or iron chelators such as desferroxamine to culture media inhibits bacterial growth and bacteria resume growth with iron replacement (18).

Less iron is available to bacteria during an infectious process due to the "iron shift" that occurs as part of the acute-phase reaction. The iron shift involves a rapid decrease in serum iron concentration with a consequent fall in transferrin saturation (19). Unsaturated transferrin could compete for available iron sources and contribute to an inhibition of microbial growth and decrease in virulence.

EVIDENCE THAT IRON MAY PROMOTE INFECTION

Over 100 years ago, Trousseau (20) observed that iron supplementation of patients with quiescent tuberculosis often led to clinical recurrence. McFarlane et al. (21) suggested that the rapid deterioration and death of infants with kwashiorkor was related to refeeding, especially micronutrient supplements containing iron. A direct correlation between serum transferrin concentration and survival was observed in a group of 40 children treated with a high protein diet, antimalarial agents, vitamins, and iron. Overwhelming infection was the most frequent cause of death. After 2 weeks of treatment, the mean serum transferrin concentration of those who survived was 130 mg/dl versus 30 mg/dl in those who did not survive. Serum albumin concentrations were also lower in those who died. Serum from infants dying of infection supported growth of *Staphylococcus aureus*, whereas the addition of purified transferrin to the cultures inhibited bacterial growth (22). McFarlane and co-workers suggested that in patients with low serum transferrin concentrations, iron therapy resulted in a high percent transferrin saturation that promoted bacterial infection. However, another explanation for these findings is that those who died had more severe kwashiorkor, as indicated by low serum transferrin and albumin concentrations.

The studies by Murray et al. (23-25) are widely quoted as evidence for a protective effect of iron deficiency on infection. In a prospective randomized trial of 137 adult Somali nomads with iron deficiency anemia, only patients with an otherwise normal nutritional status were enrolled. These subjects were given 900 mg of oral ferrous sulfate or a placebo for 1 month. Iron treatment raised serum iron and hemoglobin concentrations. In the untreated group ($n = 71$), there were 3 episodes (7.6%) of infection, compared with 36 episodes in 27 subjects (38%) in the iron-supplemented group ($n = 66$). Differences in rates of infection were noted for malaria, brucellosis, and tuberculosis. Although this study has been criticized because the follow-up time was limited and the study was not double-blinded, it is the

most convincing evidence that oral iron treatment may increase the incidence of certain infectious illnesses.

EVIDENCE THAT IRON MAY PROTECT AGAINST INFECTION

In 1928, Mackay reported the results of a survey of 541 nonhospitalized infants in London (26). She observed that anemia was common in breast-fed and cow's milk-fed infants. Oral iron supplementation not only raised hemoglobin, but allegedly reduced the incidence of respiratory and diarrheal disease by 50%, compared to untreated controls. Unfortunately, important intervening variables were not reported. Furthermore, the study compared successive years of treated and untreated populations, instead of concurrently treated and untreated groups. However, it is remarkable that Mackay recommended 60 years ago that formula-fed infants be given an iron supplement before 2 months of age and that many breast-fed infants also require iron treatment.

Twenty years ago, Andelman and Sered (27) described the effect of feeding an iron-fortified formula for 6 to 9 months to 603 infants of low socioeconomic status in Chicago and compared the results to 445 control infants fed a non-iron-fortified evaporated milk formula. Although growth was similar in both groups, 9% of the iron-treated infants had anemia compared to 76% of the untreated infants. There was also a striking reduction in the incidence of respiratory infection in the group receiving iron-fortified formula. This study has been criticized for the loose criteria defining infection and for the dependence on parental recall of illness. The same criticisms apply to a study by Burman (28) in which infants 3 to 24 months of age were randomized to receive iron or no supplementation with no difference in infection found between groups. Lovric (29) found that anemic children had a significantly higher prevalence of gastroenteritis than nonanemic controls. However, it is unclear whether the gastroenteritis is the cause or consequence of the anemia. Another study of Maori infants showed that infants who received parenteral iron dextran in the neonatal period had lower hospital admission rates during the subsequent 2 years, principally for some respiratory and gastrointestinal infections, than untreated controls (30). Randomization of infants as well as the selection of clinical end points were probably inadequate. Hospital admissions are not always based on standardized criteria, and these in turn may change over time.

Mucocutaneous candidiasis in pediatric and adult patients, associated with an iron deficit, improved when iron was administered (31,32). However, other studies have failed to show that iron status or treatment had a significant impact on either oral or genital candidiasis (33).

Oppenheimer et al. (34) showed in a retrospective study that meningitis and pneumonia were more common in the presence of iron deficiency in

hospitalized infants in Papua New Guinea. However, the effect of infection on iron status measurements is now known to be a confounding factor when attempting to establish a relationship between iron status and infection after infection has occurred. The knowledge that alterations in iron status, which mimic iron deficiency anemia, may last several days or weeks after an acute infectious episode has subsided should give us a new perspective for evaluating past and future studies (19).

PARENTERAL IRON THERAPY

Barry and Reeve (32,35) have reported the results of giving a large number of Polynesian neonates prophylactic intramuscular iron dextran. During a 2-year period, the incidence of neonatal sepsis (usually due to *E. coli*) was 22 per 1,000 infants. After discontinuing the administration of iron dextran, the incidence of sepsis decreased to 1.8 per 1,000 infants. Most infections occurred 4 to 10 days after the injection without evidence of localized infection at the injection site. Several flaws in this study detract from the authors' conclusion that iron treatment was related to the increased incidence of death from sepsis. Rates of infection prior to the use of iron dextran were not provided, and since the entire population was treated, there were no simultaneous controls. Also, it is not clear whether the iron itself or the parenteral iron dextran was responsible for the effect. Unfortunately, once this paper was published, ethical issues precluded the study of the use of parenteral iron in neonates; thus, a well-planned study could not be carried out to clarify this issue.

In contrast to the study of Barry and Reeve, no increase in susceptibility to infection was seen in a study in the U.S. in which premature infants received prophylactic iron dextran (36). Also, a Finnish study of premature infants showed markedly lower infection rates during the first 6 months of life in neonates given prophylactic iron dextran than in untreated controls (37). Additionally, before Barry and Reeve's study was published, we gave 150 mg of iron dextran to 500 newborns in a maternity hospital in Santiago, and no cases of severe infection were detected during the first 4 days of life. Unfortunately, since 10 infants were lost to follow-up, the data on infection rates were not published (M. Olivares, personal communication).

Recently, a more extensive and carefully designed prospective, double-blind, longitudinal protocol has been carried out by Oppenheimer and co-workers in Madang, Papua New Guinea, where malaria is endemic (34,38). A total of 486 newborn infants were randomized to receive either 150 mg of elemental iron as intramuscular iron dextran or a placebo at 2 months of age. After 12 months of follow-up, death rates were similar in both groups, with the primary cause of death being lower respiratory infection related to measles or pertussis. However, in the iron-treated group,

there was an increased incidence of otitis media, severe lower respiratory infections, malarial parasitemia, and splenomegaly rates. Hospital admissions associated with measles and malaria were also higher. After 6 months, 18.5% of the iron-treated group and 11.3% of controls were positive for malaria; and after 12 months, the percent positive were 33% and 20%, respectively. Nevertheless, no significant difference was found in the degree of parasitemia in the positive subjects. These carefully designed studies show that the difference in infection rates between iron-treated and non-iron-treated infants is at best marginal, except perhaps for malaria, a chronic disease for which infection rate and disease detectability are not synonymous. In the pathogenesis of malaria, a parasite that infects the red blood cell, newer erythrocytes are more susceptible to infection. Thus, it is conceivable that iron-deficient infants do not have as heavy parasitemia as the iron-replete infants and that actual infection rates are similar.

The contradictory findings reported in the literature on the interaction of iron and infection may be due to differences in the degree of exposure to infection. Most reports that support the concept of an increased risk of infection after iron treatment are based on studies of disadvantaged populations in developing tropical countries. In these populations, it is valid to assume that other nutritional deficits in addition to iron deficiency may be a factor in the susceptibility to infection. The only condition that seems to be enhanced by iron supplementation is malaria, probably due to the pathogenesis of this disease. Nevertheless, data in this regard are far from conclusive.

EFFECT OF IRON-FORTIFIED FOODS ON INFECTION DURING INFANCY

Three field studies testing the effect of iron-fortified foods on infection during infancy have been carried out in Chile. The Chilean government sponsors a supplemental food program, the National Supplementary Food Programme (NSFP), that provides free milk to children. The program has considerable prestige and acceptance. It provides 3 kg of full-fat milk per month for infants 0 to 6 months of age, then 2 kg for infants up to 24 months of age, and it reaches more than 80% of Chilean children. The milk provided by the NSFP is not iron-fortified. The children enrolled in these field studies were of middle to low socioeconomic status, living in houses built of solid material, with running water, a sewage system, and electricity.

Study 1

The study population lived in Santiago, Chile in an area served by two outpatient clinics of the National Health System (NHS). Infants for this study were selected randomly from participants in a larger field trial designed to

determine the effects of iron-fortified milk on the iron nutritional status of infants (39). The larger field trial prospectively followed infants who had received two types of milk from 3 to 15 months of age. The infants were randomly assigned to an iron-fortified milk group ($n = 198$) or a non-iron-fortified group ($n = 184$). The iron-fortified milk group received a full fat (26%) powdered milk fortified with 15 mg of iron as ferrous sulfate, 100 mg of ascorbic acid, 1,500 IU of vitamin A, and 400 IU of vitamin D per 100 g of powder. The iron-fortified product was slightly acidified (total acidity = 2.5 g lactic acid/L) in order to discourage its consumption by other members of the family. The non-iron-fortified milk was a nonacidified similar powdered product. Both milks were provided through the clinic, and there was no noticeable difference in milk consumption between groups. Solid foods were introduced to all infants according to the usual practice in Chile: fruits and juices at 2 months, vegetables and meats at 4 months, legumes at 6 months, and table foods at 9 months of age.

Partially or fully weaned 3-month-old infants were considered for inclusion in the morbidity study if they met the following criteria: birth weight > 2,500 g, and free of perinatal illness, chronic disease, malnutrition, blood transfusion, or iron therapy. Seventy-four recipients of iron-fortified milk and 76 control infants were enrolled in the study (40).

Both groups received home visits by a trained field nurse every week, and mothers were instructed to keep a daily record of symptoms and signs. A standardized form was provided to record the following: number and character of the stools (formed, pasty, liquid, mucus, or blood), cough and/or wheezing with or without fever, and nasal discharge. One episode of diarrhea was defined as the presence of liquid stools for more than 24 hr. One episode of respiratory illness was defined as cough and/or wheezing for a duration of at least 5 days. Second episodes were those occurring after 7 or more symptom-free days. Every 2 weeks, the nurse obtained information on the infant's food intake. Consumption of iron-fortified milk was confirmed by serial determinations of iron in stools.

Infants at 3, 9, and 15 months of age were seen at the clinic, where anthropometric measurements and determinations of iron nutritional status were performed. Blood sampling was delayed for those children who were clinically ill at the time of a scheduled clinic visit.

Criteria for exclusion from the study were (a) hemoglobin levels below 9 g/dl at 9 months of age; (b) failure to follow the protocol; (c) less than 45 completed morbidity forms; (d) less than the level of iron in stools previously determined as proof of consistent iron-fortified milk intake; and (e) breast-feeding exclusively for more than 120 days. Fifty cases were not evaluated due to prolonged breast-feeding. Thus, the data from 53 infants receiving iron-fortified milk and 47 receiving non-iron-fortified milk were analyzed.

The prevalence of anemia and iron deficiency was significantly less in the iron-fortified group at 9 or 12 months of age. There were no differences

between the two groups in the percentage of undernourished infants. No subjects were below 75 % of the 50th percentile of NCHS standards for weight for age. The socioeconomic conditions of the two groups were similar.

The mean number of episodes of diarrhea was 1.1 per year per child in the iron-fortified group and 1.2 per year per child in the non-iron-fortified group. The figure for lower respiratory infections was 3.9 per year per child in both groups. In the iron-fortified group, 49.1% of infants and, in the non-iron-fortified group, 38.3% never developed diarrhea. The incidence of respiratory infection was 5.7% and 10.6% for the iron-fortified and non-iron-fortified groups, respectively. All differences were not statistically significant.

The main result of this prospective controlled study was to demonstrate that iron supplementation of milk at doses sufficient to eradicate iron deficiency anemia did not result in a significantly increased incidence of diarrheal or respiratory illness.

Study 2

This regional field trial was conducted to determine if the results of the first study could be reproduced under the standard operating conditions of the NHS clinics. The premise was that replacement of the non-iron-fortified formula distributed by the NHS with the iron-fortified formula would prevent iron deficiency in the vast majority of Chilean children reached through this program.

Two groups of spontaneously weaned infants were studied between June 1978 and February 1980 in all of the NHS clinics in the central area of Santiago. Infants born before July 31, 1978 continued on the regular non-iron-fortified milk program, which consisted of 3 kg of full-fat powdered milk per month until the age of 6 months, and 2 kg/month thereafter. Infants born after August 1, 1978, were given an equivalent amount of acidified iron-fortified milk with ascorbic acid as the control group. Health care was identical for the two groups. Detailed medical and nutritional status information was collected for 585 infants born in June and July who received non-iron-fortified milk and 654 infants born in August and September who received iron-fortified milk. These infants were followed until at least 9 months of age.

At 9 and 15 months of age, laboratory tests of iron nutritional status were performed on a subsample of approximately 200 infants in each group. These subsamples were randomly selected from the infants being followed in the seven participating clinics. Infants were selected on the basis of whether they were actually consuming the prescribed milk without consideration for other demographic factors such as birth weight. Clinic personnel provided well-baby care, took anthropometric measurements, and treated illnesses.

Initially, the general characteristics of the two groups were similar. There were no differences in birth weight, socioeconomic condition, maternal age,

or parity. Breast feeding was actively encouraged at the clinics. The data on exclusive breast feeding were comparable for both groups, indicating that the introduction of the iron-fortified formula had no effect on duration of breast feeding. The percentage of infants born in August and September who actually consumed the acidified milk, excluding those who were breast-fed, varied between 70% and 80% from 3 to 15 months of age. Mothers who stated that their infants rejected the acidified milk were allowed to switch to the regular milk. It was very difficult to determine whether it was the infant or the mother who rejected the acidified milk.

There was a highly significant difference ($p < 0.001$) in all laboratory parameters of iron nutritional status between the two groups measured at 9 and 15 months of age. The percentage of iron-deficient subjects was lower in the iron-fortified group. The incidence of anemia in the iron-fortified group was 11.8% at 9 months and 5.5% at 15 months of age compared to 32.5% at 9 months and 29.9% at 15 months of age in the control group. At 15 months of age, only 3.8% of the infants who took iron-fortified milk for more than 10 months were anemic compared to 12.5% of those taking the iron-fortified milk for less than 10 months.

During the summer months of the southern hemisphere (November through February), when diarrhea tends to be prevalent, the group receiving iron-fortified milk had a lower incidence of diarrhea than the group receiving non-iron-fortified milk. The differences between the groups were statistically significant for the months of November and February. No group differences in the incidence of diarrhea were observed during the winter months. Moreover, there were no seasonal differences in the incidence of respiratory infections between the two groups.

In summary, the regional field trial confirmed the positive effect of the well-tolerated acidified, iron-fortified milk on the iron nutritional status of infants. There also appeared to be a positive effect of iron fortification on growth, particularly in low-birth-weight infants. This effect may have been due, in part, to less sharing of the acidified, iron-fortified milk within the family. In addition, the acidified, iron-fortified milk seemed to offer some protection against diarrhea in the summer months. However, the effect of the iron could not be separated from the effect of acidification.

Study 3

This study evolved from our most recently completed field trial of iron-fortified foods. In this study, infants who were being breast-fed adequately at 3 months of age were randomly assigned to one of two groups: either a group receiving heme iron-fortified rice cereal as a weaning food at 4 months of age and continuing through 12 months of age; or a group receiving the common solid foods that caregivers of Chilean infants are instructed

to use (a meat-cereal-vegetable soup, fruits, and fruit juices at 4 months, legumes at 6 months, and table foods at 9 months of age). Infants who were obtaining > 50% of their expected energy intake from sources other than human milk were assigned either to a group receiving non-acidified fortified milk with 15 mg of elemental iron as ferrous sulfate per liter of reconstituted milk plus 100 mg of ascorbic acid, or to a group receiving regular non-iron-fortified milk provided by the NHS. Each group consisted originally of approximately 100 infants.

All infants enrolled in the study were full term and essentially healthy. They were seen monthly at the clinic for checkups, anticipatory guidance, and anthropometry, and they could come to the clinic whenever they were ill. Each home was visited weekly by a field nurse who completed a dietary survey and morbidity questionnaire similar to that used in Study 1.

Growth and development were similar in all groups. Breast-fed infants tended to be heavier during the first 6 to 9 months of age, but their weights were at the 50th percentile of the NCHS by 1 year of age. Deficient iron nutritional status, as measured by low iron stores and anemia, decreased in incidence across groups as follows: the non-iron-fortified early weaned infants, unfortified breast-fed infants, iron-fortified breast-fed infants, and fortified milk-fed infants.

These results illustrate the partial protection offered infants by breast feeding and the effectiveness of feeding an iron-fortified product consumed consistently from 3 to 4 months of age.

The incidence of mild diarrhea (less than 1 day's duration), diarrhea of more than 1 day's duration, and upper respiratory or lower respiratory disease was identical in all groups (Fig. 1). Otitis media was also uncommon. Seasonal variation showed its usual influence on prevalence of diarrhea and respiratory disease, without affecting any particular set of infants (Fig. 2).

Tunnesen and Oski (41) have recently reported on the effects of feeding whole cow's milk versus iron-fortified formula to infants after 6 months of age. At 12 months of age, the 69 infants receiving cow's milk had evidence of a lower iron status as measured by serum ferritin, erythrocyte protoporphyrin, and mean corpuscular volume and an increased incidence of anemia, as compared to 98 infants receiving iron-fortified formula. There was no evidence of untoward effects. The incidence of otitis media, wheezing, nasal discharge or congestion, diaper rash, constipation or guaiac-positive stools, or hospital admissions did not differ. Diarrhea, however, was more frequent in the infants fed cow's milk. A bias in this study may be the parental decision to give cow's milk instead of an infant formula when both were provided free of charge.

In conclusion, in places where sanitation and disadvantaged living conditions markedly increase the susceptibility to infection, at least one study seemed to demonstrate that large doses of oral iron for adults and parenteral iron for 2-month-old infants moderately increased the incidence of certain

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FIG. 2. Incidence of mild, moderate, or severe diarrhea for infants in Study 3 according to seasons (Summer, Fall, Winter, and Spring) recorded in clinic visits.

illnesses, particularly malaria. However, in all of these subjects, because multiple nutritional deficiencies were not adequately controlled, these effects could not be attributed exclusively to iron. Therefore, under usual circumstances in most areas of the world, oral iron therapy is not associated with increased rates of infection. More research is needed in the use of parenteral iron preparations in infancy, particularly in regions where there is a high prevalence of malaria. All current evidence indicates that iron fortification of foods is not associated with increased susceptibility to infection; moreover, there is some evidence that an adequate iron nutritional status may be beneficial.

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Iron and Infection

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The interaction between host and infectious agent is a complex phenomenon, and no theory or experimental model has encompassed that complexity. The central focus of scientific inquiry should be to identify the basic processes and factors of both the human immune response and infectious agent virulence. When reviewing the literature on the relationship of iron deficiency to infection, one encounters conflicting data and divergent results. Some investigators favor the contention that mild iron deficiency is "good" for immunity, while others contend that any iron deficit is not good for immunity.

To examine this controversy, we will address (a) the relationship of iron to the immune response *in vitro*; (b) the evidence that administration of iron may promote infection; (c) evidence that iron may protect against infection; (d) the effect of parenteral iron therapy; and (e) the effect of iron-fortified foods on infection during infancy.

IMMUNE RESPONSE *IN VITRO*

Two immune system abnormalities associated with iron deficiency have been documented in humans: an impaired response of T-lymphocytes to mitogens and a decreased bactericidal activity of neutrophils. The DNA synthesis of T-lymphocytes in response to stimulants or mitogens results in "blastic transformation" and the production of lymphokines that are important for immune regulation. A continuous supply of iron is required for the activity of mammalian ribonucleotide reductase (1), an obligatory step in DNA synthesis (2).

Joynson et al. (3) described an impairment in lymphocyte transformation and production of migration inhibition factor after *Candida* and purified protein derivative (PPD) antigen stimulation in 12 subjects with iron deficiency anemia. Both the proportion and absolute number of T-lymphocytes were reduced in iron deficiency anemia. Lymphocyte proliferation and response

