Iron and Infection

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Iron has a central role in redox reactions and oxygen transport, and living organisms have developed efficient mechanisms for its acquisition, transport, and storage. In man, transferrin and lactoferrin are responsible for the transport of iron in the plasma and secretions, and nonfunctional iron is stored in ferritin. In order to compete with these powerful iron-conserving systems, microorganisms have developed their own iron-binding compounds, the siderophores, to assimilate iron from their environment (1).

Interleukin-1 (IL-1), a protein released by mononuclear phagocytes in response to microbial invasion, is a key mediator in the inflammatory reaction (2). It enhances the synthesis of a number of "acute phase" proteins such as fibrinogen, haptoglobin, ceruloplasmin, amyloid A protein, and ferritin. The result of increased ferritin synthesis is a block in iron release, resulting in reduced serum iron levels. This reduction in circulating iron, or hypoferremia, is one of the most constant features of infectious disease. Because iron deprivation in bacterial cultures is regularly associated with inhibition of growth, it has been suggested that iron deficiency may represent an important defense mechanism. The term "nutritional immunity" was introduced by Kochan (3) in 1973 to underline the importance of iron deprivation as a key mechanism limiting the growth of invading organisms. Because of the paucity of clinical data supporting the significance of iron deficiency or overload in determining the severity of infectious disease in man, the nutritional immunity hypothesis has remained controversial (4). This controversy is of more than academic interest, since both iron deficiency and infectious diseases are common conditions, and iron supplementation in some populations may resolve one problem while aggravating the other.

In the following, I shall discuss briefly the importance of microbial iron requirements; the role of iron in host resistance; the effect of iron deficiency and overload on clinical infection; and the control of infection by selective iron deprivation through iron chelating therapy.

MICROBIAL IRON REQUIREMENTS

The ability of pathogens to multiply in the body is dependent on their ability to acquire sufficient iron for their growth. Most pathogens obtain iron by producing
their own iron-binding compounds, siderophores, classified chemically as either phenolates or hydroxamates (1). These siderophores are able to compete successfully with the iron-binding proteins of the host.

The availability of iron is closely related to bacterial virulence (5). For example, in both Escherichia coli and Vibrio, plasmids encoding for iron sequestration systems are also determinants of virulence (6). The presence of a siderophore-binding protein on the cell surface of Pseudomonas aeruginosa is essential for its virulence (7). Neisseriae are able to develop surface receptors specific for human transferrin and lactoferrin in response to iron starvation, and only Neisseriae utilizing transferrin iron are pathogenic (8). Finally, injection of inorganic iron enhances the *in vivo* virulence of Klebsiella, Pseudomonas, E. coli, and a large number of other bacteria (9).

However, in some cases iron deprivation promotes the virulence of pathogens. Thus Corynebacterium diphtheria, Clostridium tetani, Shigella, and Pseudomonas produce their toxins optimally under conditions of iron deprivation (10). Indeed, the use of iron salts for the local treatment of diphtherial pharyngitis was a common practice in the 19th century. Thus, rather than limiting infection, iron deficiency may lead to the emergence of more virulent bacteria and potentially more serious disease.

**IRON AND CELLULAR RESISTANCE**

The effect of iron status on immune function and cellular resistance to infection has been the subject of a number of extensive recent reviews (11-13). Results of studies in white blood cells obtained from iron-deficient subjects have shown a number of abnormalities: In iron-deficient neutrophils, bactericidal activity was reduced (14) and the respiratory burst was impaired (15,16). In iron-deficient lymphocytes, activation and effector function were normal, but the proliferative response to mitogens was reduced (17,18). Antibody-mediated immunity in iron-deficient individuals appeared to be normal (11).

Neutrophils obtained from patients with transfusional iron overload showed severe impairment of phagocytosis and myeloperoxidase activity inversely correlated with serum ferritin concentrations. This could be reversed by several months of treatment with deferoxamine in the iron-loaded hosts (19,20). In another study, impaired activity of natural killer cells against target K562 cells has been shown in lymphocytes obtained from thalassemic patients. This abnormality was in direct proportion to the severity of transfusional iron overload in the donor, and was corrected by *in vitro* incubation with deferoxamine, implying that the functional impairment was a direct consequence of iron overload (21). In thalassemic mice, reduced responsiveness of splenic mononuclear cells to various mitogens has been found (22).

These observations indicate that both iron deficiency and iron overload may result in impaired function of cells associated with host defense in microbial infection, and that a normal iron status is probably the optimal condition allowing a full phagocytic and immune response to pathogens.
Conclusive evidence in favor of or against the theory of nutritional immunity should be provided by clinical studies in which the incidence and severity of infectious diseases are correlated with iron status. In the following, an attempt will be made to evaluate the available information relevant to this question.

Chronic Iron Deficiency

There are various limitations inherent to the study of infection in iron deficiency, as emphasized in a recent review by Dallman (11). A close relation exists between poverty and the prevalence of iron deficiency, and direct comparison of the incidence of infectious diseases in an iron-deficient as against an iron-replete population may be meaningless because of many other differences between such populations such as socioeconomic status, nutritional deficiencies unrelated to iron deficiency, and housing conditions. In addition, subjects with severe iron deficiency anemia must be excluded from any prospective randomized study because of ethical reasons, thus restricting the study to moderate-to-mild deficiency and possibly obscuring the effect of iron deficiency. Finally, both anemia and reduced transferrin saturation may be the consequences of infection and, unless strict criteria are applied, may result in an overdiagnosis of iron deficiency associated with infection.

Because of these considerations, it is preferable to study the effect of iron administration on the incidence and severity of infection, comparing the results with an untreated control group. Unfortunately, there are only a few studies of this sort, most of which are uncontrolled observations. A distinction should be made between oral and parenteral colloidal iron therapy, since the massive deposition of colloidal iron in the reticuloendothelial system may result in its temporary blockade.

Most reports of infections associated with parenteral iron therapy originate from tropical countries. Barry and Reeve (23) have reported both (a) an increased incidence of neonatal sepsis among Polynesian infants following the introduction of a prophylactic program of intramuscular iron dextran therapy and (b) a reduction from 22 to 2 per 1000 in the incidence of sepsis after discontinuation of the program. Unfortunately, the incidence of neonatal sepsis in this population prior to parenteral iron therapy is unknown, although mortality rates have increased after initiation of treatment (24). Because the entire population had been treated, there was no control population for direct comparison.

In another uncontrolled study by Byles and D’sa (25), the effect of total-dose intravenous iron dextran infusion was studied among Tanzanian women. The incidence of postinfusion malaria was 2.8%, but in the absence of untreated controls the proportion of subjects who might have developed parasitemia without iron treatment is unknown. More recently, a prospective randomized longitudinal study has been performed among infants in Papua New Guinea to study the effect of intramuscular iron dextran given prophylactically at the age of 2 months (26). Within the
following year the prevalence of slide-positive malaria was about 50% higher in the iron-treated group, but there was no increase in the density of parasitemia or rates of clinical malaria. In contrast to the study reported by Barry and Reeve (24), there was no difference in the rate of fatal infections between the two groups. Moreover, in a study by Cantwell (27) in which Maori newborn infants were randomly selected to receive iron dextran injections, a small but statistically significant reduction in hospital admission rates was observed in the iron-treated group.

A serious limitation of studies involving the parenteral use of colloidal iron is the unphysiologic manner of iron delivery. Parenteral iron therapy may result in serum iron concentrations exceeding temporarily the total iron-binding capacity of transferrin, and the massive deposition of colloidal iron in the reticuloendothelial system may interfere with its protective function in a manner totally unrelated to iron nutrition. Thus, although such studies may provide some information on the risks involved in the use of colloidal iron, they bear little relevance to the question of nutritional immunity.

Unlike parenteral iron therapy, treatment with oral iron medications is more physiologic and does not involve the risks of extremely high serum iron concentrations or interference with reticuloendothelial function. Several large-scale studies have been conducted among children in Western industrialized countries in which the effect of long-term iron supplementation on infection has been examined in a prospective manner. Two of these studies were randomized. Most infections encountered were common respiratory and gastrointestinal infections (28-30). One study showed no difference between the iron-treated and control groups (30), and the other two showed a reduced incidence of infectious diseases following iron treatment (28,29).

Studies of oral iron treatment in tropical countries represent a special category because the incidence and severity of infectious diseases in this environment may be much greater than in industrialized countries, and because most of the preliminary uncontrolled reports of parenteral iron treatment aggravating infection originated from such countries. In a prospective randomized study of adult Somali nomads with iron deficiency anemia (31), there was a 12-fold increase in episodes of infection in patients receiving iron compared to untreated controls. The most striking differences were in malaria, brucellosis, and tuberculosis. These dramatic effects of oral iron treatment on tropical infections have not been confirmed by other randomized studies in similar populations. In a study conducted among preschool village children in India, no significant increase in the frequency or duration of respiratory and enteric infections has been found after 12 months of iron supplementation, despite careful follow up by weekly home visits (32). Likewise, in a recent prospective randomized study of prepubescent schoolchildren in Papua New Guinea treated with oral iron, there was no difference in malarial parasite rate, parasite density, or levels of antimalarial immunoglobulin between children receiving oral iron and the control group (33).

It is difficult to reconcile these seemingly conflicting observations on the effect of iron therapy on infection. Some of the earlier reports are uncontrolled anecdotal
observations. Most of the carefully designed prospective randomized trials show no conclusive evidence of an increased risk of infection following oral iron treatment. It is recommended that in order to evaluate the effect of iron, parenteral iron preparations should be avoided, since this mode of therapy may introduce additional variables unrelated to the effect of iron per se. In view of the importance of the interrelation between iron administration and the risk of infection, additional studies exploring this question in various populations are greatly needed.

**Chronic Iron Overload**

Idiopathic hemochromatosis, chronic renal failure, and thalassemia major are often referred to as clinical conditions in which iron overload is responsible for an increased incidence of infections. However, it is difficult to distinguish the effect of the underlying morbidity associated with these clinical entities from the direct effect of iron on infection.

In the precirrhotic phase of idiopathic hemochromatosis, infection is not a significant problem. Mortality among terminal patients is mainly caused by hepatic or cardiac failure, hepatoma, and diabetes (34). Pneumonia is a terminal event in 12% of patients, but with coexistent cirrhosis and diabetes this can hardly be attributed to iron alone.

There is an increased incidence and severity of bacterial infections in patients maintained on chronic hemodialysis. Several investigators have shown that infection is more common in patients with increased ferritin levels (35,36), and it was suggested that iron overload may be the main cause of the observed increased susceptibility of hemodialysis patients to bacterial infection. However, the observed ferritin values, ranging from 500 to 2000 μg/l, are much lower than the range of values observed in other conditions associated with severe transfusional iron overload. It is quite likely that the increased transfusion requirement of these patients is indicative of an increased severity of the underlying disease and that there is no cause-and-effect relationship between increased ferritin measurements and infection. With the introduction of regular erythropoietin support to such patients, it would be interesting to examine whether such treatment leading to improved hemoglobin and reduced ferritin levels may also result in a reduced susceptibility to infection.

In homozygous β-thalassemia, severe infections are responsible for about 20% of deaths. Because transfusional iron overload is a major problem in many of these patients, thalassemia appears to be an important illustration of the role of iron overload in infection. However, a close examination of risk factors of infection in thalassemia shows that other variables may be more important. Among patients in two major series reported from the USA and Great Britain, all but two fatal infections and all severe infections such as meningitis, peritonitis, and osteomyelitis occurred in splenectomized patients (37,38). The increased risk of infection in splenectomized thalassemic patients may be explained by a reduced response to circulating antigens and the reduced clearance of bacteria associated with asplenia (39). Anemia is a
second important risk factor of infection in thalassemia. In the British series the incidence of pneumonia in anemic patients was eight times higher than in well-transfused patients, with hemoglobin values ranging from 10 to 14 g/dl. In contrast, the risk of infection in thalassemic patients is unrelated to age (which is an indirect indicator of transfused iron burden) or to the severity of iron overload. Of the 10 thalassemic patients with fatal infections described by Modell and Berdoukas (38), four were well-chelated patients and in three others the total estimated iron load was less than 5 g. Thus, although infection is an important complication of thalassemia, there is no convincing evidence that iron overload has a major role in its causation.

EFFECT OF IRON CHELATION

The belief that iron depletion may suppress the proliferation of pathogens has generated an interest in the therapeutic potential of iron-chelating agents. If pathogens are dependent on iron for their unimpeded growth, it might be possible to interfere specifically with their proliferation by the use of selective iron-binding agents. Several recent studies have shown that this may be feasible. In vitro and in vivo studies with Trypanosoma cruzi (40), Pneumocystis carinii (41), Legionella pneumophila (42), Plasmodium falciparum, P. vinckei and P. berghei in mice, rats, and monkeys (43–46) have shown that it is possible to inhibit the proliferation of these microorganisms by the iron-chelating agent deferoxamine. Subsequent in vivo studies with P. berghei have shown that parasite inhibition is independent of host iron status, and that the therapeutic effect of deferoxamine is explained by its direct interaction with a chelatable labile iron pool within the infected erythrocyte. It is assumed that parasite inhibition is caused by inactivation of ribonucleotide reductase, an iron-dependent rate-limiting enzyme in DNA synthesis (47). Because the ability of deferoxamine to penetrate the red cell membrane is limited, other iron-chelating compounds with a higher lipid solubility have been studied and several of these have shown improved antimalarial activity (48). Preliminary studies in patients with asymptomatic P. falciparum parasitemia, and in children with cerebral malaria conducted in Zambia (G. Brittenham, personal communication), have shown that deferoxamine given by continuous infusion at 100 mg/kg/day for 72 hours results in (a) the complete disappearance of parasites from the circulation and (b) a significant shortening of the duration of altered consciousness.

Studies on the intracellular biology of L. pneumophila in human monocytes have shown that activated monocytes are able to limit the availability of iron for invading organisms by down-regulating the number of transferrin receptors on the cellular surface (42). In addition, the sharp increase in apoferritin synthesis induced by inflammation may result in a shift of labile intracellular iron to the relatively unavailable compartment of ferritin iron stores (49). Thus the alterations in iron homeostasis associated with inflammation may limit the availability of intracellular iron for invading organisms by reducing transferrin iron uptake as well as by diverting the labile iron pool into relatively unavailable storage compartments. Deferoxamine may
represent a compound which simulates this intracellular protective mechanism. Comparison of all available in vitro studies on the antimicrobial effect of deferoxamine and other chelators reveals a striking similarity in the inhibitory concentration of these drugs. Without exception, the inhibitory concentration is about 20 μM, and a maximal effect is achieved between 40 and 100 μM. These figures may represent the approximate magnitude of the intracellular chelatable iron pool.

These intriguing new observations on the antimicrobial effects of deferoxamine and other iron chelators lend new meaning to the term "nutritional immunity" and open new channels for exploring the possibility of controlling infection by means of selective intracellular iron deprivation. Experimental models for studying the effect of iron chelators on other intracellular pathogens such as Toxoplasma gondii, Chlamydia psittaci, Mycobacterium tuberculosis, and Leishmania species should be established. Packaging the chelator in liposomes or red cell ghosts, or manipulating their lipid solubility to improve their delivery to appropriate target organs such as the macrophage system, may greatly improve their efficiency. In view of its short half-life and poor oral effectiveness, it is unlikely that deferoxamine per se will be suitable for clinical use as a practical antimicrobial agent. However, with the introduction of simple, orally effective new chelators, it is reasonable to expect that future research may lead to the identification of iron chelators with considerable usefulness in the control of infectious disease.

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DISCUSSION

Dr. Adelekan: Although the controversy surrounding the interaction of iron and infection remains largely unresolved, I have a hypothesis that could be used as a basis for discussion. The main evidence that iron deficiency has a protective effect against infection comes from the hypoferremia which constantly accompanies infection or inflammation. This has been interpreted as indicating an interruption of iron supply to the invading pathogen as part of the defense mechanism, starving the pathogen of much needed iron. We know, however, that there are pathogenic bacteria which do not need iron and which become more virulent in the absence of iron. The protective effect of iron deficiency is therefore not entirely due to starving the invading pathogen of iron.

The hypothesis I am trying to promote is that the hypoferremia that we see in infection is a host response to clear iron from the circulation into the reticuloendothelial stores, thus minimizing the initiation of free radical reactions. We know that polymorphonuclear leukocytes produce superoxide and hydrogen peroxide as part of the host reaction to infection. These two radicals are not very damaging in themselves, but in the presence of free iron they combine to form the highly reactive and damaging hydroxyl radicals. Hydroxyl radicals cause extensive damage to the tissues, thereby making them more susceptible to the infection. If the damaging effects of the free radicals can be minimized, the ability of the host to resist infection would be likely to be enhanced and it would not matter much whether the invading pathogen has a supply of iron or not.

Dr. Hershko: The question whether the hypoferremia of infection is a useful phenomenon is almost a religious one. If you believe that everything that God created is useful, then it is useful, but that is not the question I was trying to answer. However, whether iron deficiency has a protective effect is a very practical question because we do not want to find ourselves setting out to resolve one problem and creating another, particularly in populations with high rates of infection. The situation in vivo is much more complex than in vitro. Low serum iron
may be deleterious to bacteria, but at the same time it may interfere with macrophage and lymphocyte function and you end up with a balanced situation where there is no net effect on the host. The question is, Is there any good clinical evidence from controlled trials that the correction of iron deficiency involves risk of aggravating infection in children or adults? The bottom line from all the available published reports is no. However, the controversy is likely to continue because some people are very committed to the theory. The deferoxamine study is a different issue and may lead somewhere in the future, though I would not like to give the impression that I am advocating deferoxamine for treating infection at this stage.

Dr. Dufour: You showed results of a study using chelating agents in humans. Were the iron status and general nutritional status of the patients determined before they were given the chelating agent?

Dr. Hershko: This paper has not been published yet, but I have seen the draft. The patients were adults with normal nutritional status. The only variable examined was the extent of parasitemia. The administration of deferoxamine in a dose of 2 g/day (about 40 mg/kg) had no toxic effect but caused a very reproducible reduction in parasite counts. This is the first study in which animal data have been confirmed.

Dr. Finch: The description of the action of chelate inside the red cell tying up essential iron brings to mind the analogy of the action of deferoxamine in iron absorption. If you give it parenterally, it enters the gastrointestinal mucosa and blocks absorption from the gut lumen. One might speculate that the fraction of iron you identify is the same one as is involved in the active transport of iron across the mucosa.

Dr. Hershko: I agree. One of the most difficult things to measure is the chelatable intracellular pool, because you don't know what it is bound to. It is almost impossible to fractionate the cell, so this is a very elusive topic in iron research. However, it is interesting to know that in all of these studies the critical inhibitory concentration was almost identical whatever the cellular model used, and it always ended up with this magic figure of 20 μM. This is probably the first information we have about this mystical chelatable intracellular pool which has one role in absorption and another in infected erythrocytes, but has the same magnitude in both.

Dr. Adelekan: In severely malnourished children it has been shown that pathologic changes like edema take longer to resolve when they are given iron. This is believed to be due to iron catalyzing free-radical-mediated reactions in these children. Would you still recommend giving iron to a severely malnourished but iron-deficient child?

Dr. Hershko: I think I would accept that in extreme circumstances such as the one you describe, it would be unwise to give parenteral iron when we know that free iron may promote the growth of certain bacteria. In a near-normal population it is a different story.

Dr. Mejia: The relation of iron and infection is a very important topic for developing countries. Several years ago we conducted a study in Guatemala in which we supplemented children with iron. Those who received iron had a higher rate of dermal infection and our hypothesis was that increased iron in sweat combined with poor sanitation encouraged bacterial growth. Though the study was not designed to study infection, it was interesting to find there was a very clear difference between the iron-supplemented and control groups in this regard.

Dr. Adelekan: It is certainly important to take into account the environment of the patient when deciding whether or not to treat iron deficiency. It has been shown that when iron is given to children in an unhygienic environment it stimulates infection, whereas iron given in a relatively clean environment does not. This is a dilemma for people working in developing countries.
Dr. Cook: Many people at this conference have been involved in intervention trials showing that if you give iron to a population with iron deficiency anemia they will improve hematologically. If we compare what is happening worldwide with regard to iron intervention with the advances that have been made with other micronutrients such as vitamin A or iodine, the overall progress has been extremely limited. This seems to be because of concerns about the possibility of increased risk of infection. It is clear from what has been presented here that there is little, if any, support for the view that iron supplementation or fortification increases infection risk. The concern about iron and infection is strongly felt in many developing countries, and it seems unlikely that we shall make any inroads into improving iron nutrition until such concerns are laid to rest. I consider this to be one of the most important issues to be raised at this conference.

Dr. Brabin: We are taking a global view of the interaction between iron and infection. I think some of the effects of iron deficiency may vary according to the prevalence of endemic infection in a particular community. If we consider, for example, a problem such as glucose-6-phosphate dehydrogenase deficiency, it is known that it is advantageous to have this disorder if you live in a malarial zone. Maybe it is advantageous to be iron-deficient if you live in an area with a particular pattern of endemic infection. The corollary of this is that the iron status of a community may be the determinant of the types of infection in that community. For instance, it has been reported that in very malnourished children bacterial meningitis is unusual. We must be careful about making too broad assumptions in areas that may have widely different patterns of endemic infection.

Dr. Hershko: These doubts reflect the difficulty in dispelling the existing view. You would agree that the evidence for there being any risk in correcting iron deficiency is very weak, in fact almost nonexistent, but a negative study is more difficult to accept as the definitive answer because someone may always stand up and say yes, with this particular population, with this particular method, with this particular infection, you did not find a difference, but with another infection and another population maybe you will find a difference. I have no definitive answer to that, so there is a need for more carefully designed prospective studies, preferably in different countries, in different environments, and so on. It is worth emphasizing, however, that recent studies from tropical countries have shown that iron treatment does not affect malaria. I believe that so far there is no good evidence that iron is ever harmful except in a few patients in extreme situations such as kwashiorkor.

Dr. Viteri: I think there is overwhelming evidence that oral iron administration is not associated with increased rates of infection except under very special circumstances. Given this evidence I believe we can work to promote the use of oral iron to correct iron deficiency everywhere. We have two alternatives for doing this. The first is to give relatively large supplements for short periods; the second is to give small-dose fortification over long periods. On a scale of risk of 1 to 10, our experience has been that iron fortification in tropical areas has a risk of 1 or less. In tropical Guatemala, where we have given oral iron supplementation to preschool children in a dose of 3 mg/kg, we have seen no evidence of increased diarrhea or other infections in a double-blind placebo-controlled prospective study, even though we looked carefully for it. If iron supplementation is to be opposed, it must be opposed on the basis of the positive identification of increased infection risk. We should continue to supplement until it is shown to be harmful, and it seems increasingly unlikely that this will be the case.

Dr. Koletzko: With regard to children with malnutrition, I am concerned that iron supplementation carries a genuine risk from increased peroxidation. Iron, especially in combination with ascorbic acid, is a very important stimulator of peroxidation, and malnourished
children have poor antioxidant status with low vitamin E levels and reduced amounts of essential fatty acids in membranes. A further increase in peroxidative damage could be a serious problem. Another potential problem is that malnourished African children are often zinc-deficient, and this may be aggravated by adding iron in the first stages of treatment.

**Dr. Viteri:** Severely malnourished children require special attention, but I don't think the establishment of iron fortification programs will be harmful for this group. I doubt whether anyone has evidence that such supplementation is associated with any biochemical indicators of excessive peroxidation. The only evidence I know of has been obtained in extreme circumstances, for example in the studies by Wu et al. (1) in which they gave malnourished rats huge amounts of iron. I think the pursuit of such phantoms does more harm than good. We must prove any deleterious effects of oral iron administration to the population as a whole before we stifle efforts to control iron deficiency.

**Dr. Fomon:** Although I know this is an unpopular recommendation, I believe that breast-fed infants in industrialized countries (I have no experience in developing countries) should be supplemented with iron from the early weeks of life. The recommendation is not made to improve iron nutritional status during the first months of life but to improve it during later infancy. To assure good iron nutritional status at 12 months, an infant must absorb about 200 mg of iron during the first year. If this is averaged over the entire year, the infant must absorb about 0.55 mg/day. A breast-fed infant with human milk as his sole source of iron will consume about 0.33 mg of iron per day. If he absorbs 50% of this (0.17 mg/day) he will retain about 20 mg in the first 4 months of life. He must therefore absorb about 180 mg during the next 8 months—more than 0.7 mg/day. It is difficult for an infant to meet the 0.55 mg figure for absorbed iron, and it will be appreciably more difficult to meet a figure of 0.7 mg/day.

**Dr. Dallman:** I don't oppose giving iron during the first 4 months, but starting iron-fortified formula at about 4 months also seems a safe alternative for term infants. Heinrich's studies (2) showed that fasting iron absorption of trace quantities is much lower during the first few months, when iron stores are high, than later on, when they are lower. Iron absorption from infant formula can be remarkably high after iron stores are depleted and there is an increased need for iron. This was shown in a study by Gorten and Cross (3) in which preterm infants who had developed iron deficiency anemia recovered rapidly simply by changing from an unfortified to an iron-fortified formula.

**Dr. Fomon:** The statement is often made that young infants are able to absorb very little iron, but I don't know of any evidence to show that this is actually the case.

**Dr. Hashke:** There are several clinical studies that have compared iron nutritional status of breast-fed infants and infants fed formulas fortified with iron during the first 4 months of life. With the methods presently available there appears to be no difference in iron nutritional status. We need more sophisticated methods to find out whether there is really a problem in breast-fed infants in the first 4 months.

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