Committee on Nutrition

Relationship Between Iron Status and Incidence of Infection in Infancy

Iron deficiency is a common problem in infancy, but it can be prevented by the use of iron-fortified infant formula, iron-fortified infant cereals, or prolonged breast-feeding. The current recommendations for iron nutrition are summarized in a statement by the Committee. Prevention of iron deficiency is universally accepted as being worthwhile; however, during the last few years there has been increasing concern that the administration of iron can be harmful under some circumstances. The hypothesis that an iron-rich environment in the host predisposes to infection has raised questions about the safety of large parenteral doses of iron as well as the smaller amounts present in iron-fortified foods.

One possible basis for a relationship between the administration of iron and infection is the bacteriostatic effect of the iron-binding proteins transferrin and lactoferrin, which are present in serum as well as in breast milk and cow's milk. These proteins are believed to inhibit the growth of bacteria by their ability to bind iron so tightly that inadequate amounts are available to support the growth of microorganisms. Microorganisms also produce iron-binding substances that facilitate the accumulation of the iron necessary for their growth and proliferation. It is argued that a major factor in host resistance is how effectively the host's iron-binding proteins can withhold iron from the bacteria.

During the last ten years, a large body of in vitro evidence has been accumulated which indicates that the bacteriostatic properties of transferrin and lactoferrin are diminished or obliterated when these iron-binding proteins are saturated with iron. In vitro studies, using parenteral iron in experimental animals, have shown decreased resistance to bacterial infection. The results of these studies have been difficult to extrapolate to clinical situations in man, where evidence for a cause-and-effect relationship is often tenuous and where other variables may play a more important role.

IRON STATUS AND INFECTION

The purpose of this report is to evaluate the data linking iron status to infection in relation to currently recommended practices in the fortification of foods with iron. Four aspects of this problem will be considered: (1) the relationship between increased serum iron levels and predisposition to infection, (2) the role of the lactoferrin in human milk in the prevention of gastrointestinal infections in the low-birth-weight infant, (3) the effect of iron deficiency on susceptibility to infection, and (4) the effect of supplemental iron on the incidence of infection in early infancy.

Serum Iron and Infection

On the average, serum transferrin is about one-third saturated with iron in adults and somewhat less in children; however, there are severe fluctuations that depend on the time of day as well as many other factors. Iron supplementation at currently recommended doses for infants seems to have no more than a small effect on transferrin saturation. This can be inferred from several studies in which serum iron and iron-binding capacity were compared in groups of infants who were either unsupplemented or who were receiving iron supplementation at a level equivalent to or exceeding 2 mg/kg/day in preterm infants and 1 mg/kg/day in term infants. The difference in transferrin saturation between unsupplemented and supplemented groups averaged 3% to 10%, and in no instance did transferrin saturation average more than 30%.

In vitro evidence of decreased bacteriostatic activity has generally been shown with a transferrin saturation exceeding 60% or 80%. Consequently, the modest elevation in serum iron level that can be anticipated with iron fortification of foods is unlikely to be of theoretic concern in normal individuals. A possible exception to this generalization might apply to newborn infants within the first two weeks of life when iron-
binding capacity may normally become saturated. Because iron stores are ample during the newborn period, there is no urgency to administer supplemental iron during the first two weeks of life. However, there is no epidemiologic evidence that iron administration during this period would have any effect on infection at the concentration of about 12 mg/liter present in iron-fortified formulas. Thus, there is no contraindication to the initial use of an iron-fortified formula.

The use of iron-fortified foods in the presence of infection deserves separate consideration. Infection and chronic inflammation result in a depression in serum iron level and frequently in the transferrin saturation. This is primarily caused by a decreased release of iron from the reticuloendothelial system, and to a lesser degree by diminished absorption of iron from food. It is postulated that these changes augment the resistance of the host to bacterial infection.

Is it advisable to discontinue supplemental iron for those infants who contract infections? This is probably unnecessary because (1) relatively modest amounts of iron are present in most fortified foods, (2) iron absorption is probably decreased during infection, and (3) the major source of serum iron is the reticuloendothelial system rather than the diet. There are scattered reports that administration of parenteral iron in the presence of an infection can result in worsening of the patient’s clinical condition. The pertinent papers are reviewed in detail by Pearson and Robinson. Although it is difficult to come to any firm conclusions, it seems prudent to provide iron orally only, except for special indications.

**Lactoferrin and the Prevention of Gastrointestinal Infections**

Lactoferrin is an iron-binding protein present at a concentration of about 4 gm/liter in human milk, but less than 0.2 gm/liter in cow’s milk. It has a molecular weight of about 77,000, which is similar to that of transferrin. Normally, breast milk is about one-third saturated with iron (about 1 mg of iron per liter of milk); in this unsaturated state it suppresses the growth of many types of bacteria under in vitro conditions.

Lactoferrin may play a role in the suppression of bacterial growth in the infant’s intestinal tract. From a teleologic viewpoint, an additional bacteriostatic agent might be valuable in early infancy when concentrations of serum immunoglobulins are normally low. If lactoferrin were to play such a role, it would have to remain unsaturated, a condition that might not be satisfied when iron medication or iron-fortified cereal is given simultaneously with breast milk.

The possibility that lactoferrin in milk plays a bacteriostatic role in the infant’s intestine was suggested by Bullen et al. On the basis of in vitro experiments with human breast milk and in vivo studies with newborn guinea pigs, they proposed that lactoferrin in combination with specific antibodies against *Escherichia coli* has a bacteriostatic effect in the intestinal tract. For lactoferrin to play this role, it would have to pass undenatured and undigested into the infant’s intestinal tract. This possibility is favored by the observation that the pH of the stomach contents of breast-fed infants remains relatively high (pH 6 to 6.5) for about one hour after a normal feeding. The slightly alkaline pH of the small intestine favors the bacteriostatic action of lactoferrin; in vitro studies have shown this effect to be most potent at a pH higher than 7.2. The preservation of lactoferrin in the intestinal contents may be favored by the presence of a trypsin inhibitor in human milk, which would tend to delay the digestion of this protein. If the lactoferrin-iron complex remained intact in the small intestine, one might anticipate that this would retard iron absorption. Yet, the iron in human milk is remarkably well absorbed by infants, despite its high concentration of lactoferrin.

When banked breast milk is used, the lactoferrin may be denatured by pasteurization. In an earlier study, heating milk filtrate to 56°C for 30 minutes had no effect on its bacteriostatic properties, possibly because lactoferrin and casein (a major protein in milk) can form a high-molecular-weight complex that is extremely heat-resistant. However, more recent experiments indicated that similar conditions of heating resulted in loss of more than half the lactoferrin and iron-binding capacity, as well as a severe increase in its capacity to support the growth of *E. coli*. The manner in which lactoferrin and specific antibody can interact synergistically is unresolved, but it is noteworthy that milk is much more bacteriostatic than corresponding amounts of purified lactoferrin. Furthermore, free iron can also reverse the bactericidal effect of specific antibody.

The relatively low lactoferrin content of cow’s milk is probably further decreased in the processing of infant formulas because the original protein content is reduced by about 50% to approximate the protein concentration of human milk. Recent studies with a widely used commercially available cow’s milk formula showed no inhibitory effect on the growth of several strains of *E. coli* when...
compared to fresh, unprocessed human or bovine milks. The addition of iron (12 mg/qt) did not change the rate of growth of E. coli in this formula.22 The possibility that lactoferrin plays an important bacteriostatic role requires further study.

At present, we know too little about the role of lactoferrin in the human intestine to warrant modifying present methods for the prevention of iron deficiency in infancy. If unsaturated lactoferrin is found to play a bacteriostatic role in infants, it may prove advantageous to avoid feeding iron-fortified cereal or iron drops at the time of a breast-feeding. Many provocative and interesting questions have been raised, and these deserve investigation.

Iron Deficiency and Susceptibility to Infection and Host Defense

Studies in young children and adults indicate that both cell-mediated immunity and bactericidal activity of neutrophils are impaired in patients with iron-deficiency anemia.23-26 Although the phagocytic function of the neutrophil may be normal, bacterial killing is diminished.18 Neutrophils are defective in reducing the dye nitroblue tetrazolium, suggesting the possibility that an iron-containing enzyme required for this reduction may be present in diminished amounts. After administration of parenteral iron, the bactericidal abnormalities and the nitroblue tetrazolium test were corrected within four to seven days, before the hemoglobin concentration would have increased appreciably. Thus, some effect of iron deficiency other than anemia is responsible. Similar findings have been reported by other workers.24-28 However, another study of iron-deficient children suggests that there is no major defect in the function of lymphocytes or polymorphonuclear leukocytes in uncomplicated iron deficiency.29 This study is difficult to interpret because, in seven of eight children, hookworm infestation was presumed to be the major etiologic factor, and anemia resulting from blood loss might have different consequences than anemia associated with nutritional deficiency. Masawe et al.30 recently proposed that iron deficiency might actually protect against infection. They found that patients with iron-deficiency anemia had a lower incidence of infection than those with other forms of anemia. Also, there was a tendency for malaria to flare up when the iron deficiency was treated.30,31 Although these studies provide insufficient evidence to conclude that iron deficiency protects against infection, they do raise the possibility that parenteral iron administration may aggravate a latent infection.

The preponderance of evidence indicates that iron deficiency increases the risk of infection, depending on the severity of the iron deficiency23 and, possibly, on whether the cause of the deficiency is nutritional deficiency or blood loss.29

Supplemental Iron

There is no evidence that iron fortification as currently recommended1 increases the risk of infection. Most of the relevant studies compare infants receiving iron supplementation in formula with those who are unsupplemented. Andelman and Sered3 prospektively compared the effects of iron-fortified and unfortified cow's milk formula in two large groups of infants from a low socioeconomic population. Data on growth, iron metabolism, and incidence of respiratory infections were recorded for 18 months. Iron deficiency developed in 76% of the infants not receiving iron but in only 9% of those receiving the iron-supplemented formula. Significantly fewer respiratory infections occurred in the infants who received iron compared with those who did not. These authors cite six other studies with similar conclusions. However, they failed to define the criteria used for the diagnosis of infection, and there was no mention of enteric infections. Data collection depended on recollections of illness by parents over a long interval, and their reliability could be questioned.

Subsequently, a similar study by Burman32 involved two groups of infants in England, one receiving iron supplementation and the other not. During the study period (between 3 and 24 months of age), there was no relationship between the incidence of infection and iron supplementation. This study suffers from similar methodologic defects, with data based on parent recall and a lack of criteria for infection.

Premature infants have a higher incidence of infection than those born at term; in one study, one of four premature infants required hospitalization for infection in the first year of life.33 Unless given supplemental iron, most premature infants will develop iron deficiency anemia after about 3 months of age. In one study, prevention of iron deficiency did not change the rate of infection during the first year.31 In contrast, a group of Finnish premature infants given early iron therapy had only half as many infections before 6 months of age as infants who did not receive iron.34 Taken individually, these studies are difficult to interpret; however, none of the studies
suggest that iron supplementation is associated with an increased incidence of infection, only that there is either no change or a decreased incidence of infection.

CONCLUSIONS

At present, there is no evidence to warrant modification of the recent recommendations of the Committee for the prevention of iron deficiency in infancy. The benefits of supplementation seem to outweigh the possibility of iron excess during a period of development characterized by marginal iron stores. Except for the first two months of life, iron stores in children are proportionately much lower than in the adult, and iron balance may be more precarious. Unless carefully controlled clinical studies provide evidence to the contrary, iron fortification of formula and foods seems to provide safe and effective methods for maintaining iron stores and preventing iron deficiency in infancy. The benefits of prolonged breast-feeding are emphasized not only for the prevention of iron deficiency but also because of the nutritional and immunologic properties of human milk.

COMMITTEE ON NUTRITION

Lewis A. Barness, M.D., Chairman; Alvin M. Mauer, M.D., Vice-Chairman; Arnold S. Anderson, M.D.; Peter R. Dallman, M.D., principal author; Gilbert B. Forbes, M.D.; Buford L. Nichols, Jr., M.D.; Claude Roy, M.D.; Nathan J. Smith, M.D.; W. Allan Walker, M.D.; Myron Winick, M.D.

Consultants: William C. Heird, M.D.; O. L. Kline, Ph.D.; Donough O'Brien, M.D.

Supported by FDA contract 223-76-2091.

REFERENCES


ACKNOWLEDGMENT
The Committee wishes to acknowledge the assistance of Howard A. Pearson, M.D., in preparing the manuscript and Paul Saltman, Robert L. Baehner, John N. Lukens, and William Krivit in reviewing the manuscript.

BREAST-FEEDING REDISCOVERED

This poster was used in 1918 to point out the value of breast-feeding, especially to the underprivileged classes. The title is "Effect of Feeding and Social Standing on Infant Mortality." On the left is shown the mortality for 100 breast-fed babies ("Brustkinder"); on the right, mortality in 100 bottle-fed babies ("Flaschenkinder") in well-situated (I), middle-class (II), and underprivileged (III) classes.


IRON STATUS AND INFECTION
Relationship Between Iron Status and Incidence of Infection in Infancy

*Pediatrics* 1978;62;246

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/62/2/246