Prevention of Iron Deficiency

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Infants and children need to absorb about 1 mg of iron per day. This is a disproportionate requirement, compared to adults, that derives from growth. Children consume less food than adults and their diet often consists of foods with little iron content and poor iron availability. This is the challenge that needs to be met in the prevention of iron deficiency in early life.

Evidence is accumulating that iron deficiency may be associated with impaired function of various tissues (1). In the light of this knowledge, the objective of prevention during infancy and childhood should be not only to avoid the occurrence of anemia, but also to assure an adequate supply of iron to all tissues during this critical period of development.

Ideally, prevention of a nutritional deficiency should be attained by the consumption of a good diet. Unfortunately, in the case of iron, this is not always possible, and it may be necessary to fortify the diet or give iron as a supplement. In this chapter, I shall briefly review the various interrelated approaches to the prevention of iron deficiency in infants and children. The importance of adequate dietary practices and of avoiding excess iron losses will be emphasized; the options of food fortification and iron supplementation will then be discussed.

DIET

There are marked geographic (2) as well as socioeconomic (3) differences in the prevalence of iron deficiency that indicate the importance of the quality of the diet. Due to the high iron requirements in infancy and the relative monotony of the infant diet, with milk being the main source of calories, iron deficiency tends to be prevalent even in developed countries, especially in lower socioeconomic populations. After the first year of life, the child starts consuming the regular household food and, at this time, the marked differences in iron content and iron availability between different diets become apparent. Nutritional iron deficiency in preschool and school-age children in developed countries is relatively uncommon but is still highly prevalent in the poorer population groups of Latin America, Africa, and Asia.

The bioavailability of iron from different foods and diets varies considerably. Of great importance is the chemical form in which iron is presented to the intestinal mucosal cell. Several studies (4,5) have demonstrated that iron enters into two
“common pools” that behave differently in terms of absorption, the so-called heme-iron and nonheme iron pools. Heme iron, present in hemoglobin and myoglobin, is well absorbed and is relatively unaffected by diet composition (6–8). Nonheme iron, the form of iron present in vegetables, cereals, and in some foods of animal origin that are of importance in infantile nutrition, such as milk and eggs, generally is poorly absorbed and is greatly affected by enhancing or inhibiting substances in the diet (7). Some of these are listed in Table 1. Since most food iron is nonheme, the presence or absence of these substances plays a vital role in the availability of dietary iron.

An important advance in our knowledge of the contribution of the diet to iron nutrition is the role of breast-feeding. Even though the iron content of human milk is low, it is much more available than the iron in cow’s milk (9,10). As a consequence, infants that are breast-fed have an advantage over artificially fed infants in the initial few months of life (11). However, after 4 to 6 months, even breast milk cannot supply the needed iron and the infant must rely on the introduction of other foods and on supplementation to meet requirements.

It is not possible to prevent iron deficiency in all cases with diet alone, at least in infancy. However, in the light of the preceding discussion, a few recommendations can be made. First, breast-feeding should continue in all infants for at least 6 months. Second, when solid foods are introduced, proper consideration should be given to our present knowledge of dietary factors affecting iron absorption and, when possible, foods containing heme iron and/or enhancers of nonheme iron absorption (meat, ascorbic acid) should be offered. Third, foods that markedly inhibit absorption, such as tea, should be avoided.

AVOIDING EXCESS IRON LOSSES

Physiological iron losses are relatively fixed and unaffected by the iron status of the individual. However, pathological conditions, some of which are very common in many areas of the world, can markedly increase the loss of iron, particularly via the gastrointestinal tract.

The most studied and best documented cause of excessive iron loss is parasitic infection, a condition frequently occurring in preschool and school-age children in tropical areas (12). Infants with acute diarrhea may also lose significant amounts

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of blood. The cumulative loss of iron resulting from repeated episodes of gastrointestinal infection can be very significant (13). Improvement of sanitary conditions in areas with a high prevalence of diarrhea and parasitic infection will obviously contribute to the prevention of iron deficiency.

Another factor contributing to excessive blood loss in infancy is the use of fresh or pasteurized cow's milk (14,15). This phenomenon decreases with heat treatment of the milk and seems to be of importance only in the early months of life. Present recommendations are to avoid the use of fresh cow’s milk in the feeding of infants at least during the first 6 months of life (16,17).

FOOD FORTIFICATION

Food fortification is the preferred way of preventing iron deficiency in infants and in those children whose regular diet does not provide enough available iron.

The principles behind successful food fortification with iron have been extensively reviewed in recent publications (18–20).

A suitable vehicle must first be chosen. Ideally, the food vehicle should be regularly consumed by the target population in amounts that do not vary considerably between different individuals so that a level of fortification that is adequate for most of the population can be selected. It should, at some stage, be centrally processed so that iron can be added to it, and the organoleptic characteristics and shelf-life should not be noticeably changed by the fortification process. The iron preparation used for fortification should be relatively inexpensive and easy to incorporate. Most importantly, it should have a good bioavailability, an obvious fact that was not always considered in the past. Several soluble ferrous salts and reduced iron of small particle size seem to conform to these requirements (19).

The iron bioavailability from the fortified product must be studied in humans. Its efficacy should next be demonstrated in pilot field studies. Finally, if the product is to be used in a program (local, regional, national), its effectiveness must be demonstrated under the regular operating conditions of the program.

Infants

Milk-based formulas and especially prepared infant cereals are the most commonly used iron-fortified products in infancy.

There are many commercially prepared iron-fortified infant formulas on the market. They are basically cow’s milk that has been modified to resemble human milk. Most contain about 12 mg iron per liter of formula, in the form of ferrous sulphate (21).

The first demonstration in the field of the effectiveness of iron-fortified milk is the study by Marsh et al. (22). These authors gave a small number of term and preterm infants from 0 to 9 months of age a milk-based, commercially prepared formula, containing 12 mg/liter of elemental iron as ferrous sulphate. This formula also contained 55 mg/liter of ascorbic acid. Two additional groups received the same formula without iron, and evaporated milk. No solid foods were recommended
until 9 months, but some infants did receive a cereal preparation without iron. Mean hemoglobin concentration at 9 months in term infants was 12.69 g/dl in the fortified group versus 10.46 g/dl and 9.67 in the groups receiving the unfortified formula and the evaporated milk, respectively. Corresponding figures in premature infants were 12.49 g/dl for the fortified-formula group and 9.40 and 8.55 g/dl for the other two groups, respectively. There is no information on the distribution of hemoglobin values in this study, therefore the incidence of anemia in the different groups cannot be calculated.

Andelman and Sered (23) used the same product in a large number of predominantly nonwhite infants of very low socioeconomic condition in the city of Chicago. The fortified formula was given from discharge from the hospital or from the first clinic visit until 6 to 9 months of age. A control group received evaporated milk. Both groups were given strained foods at 3 months and cereals, eggs, meat, vegetables, and fruits at 6 months. At about 1 year of age, mean hemoglobin concentration was 11.9 g/dl in 321 infants who had received the fortified formula and 10.4 g/dl in 143 infants in the control group. A very high percentage (76%) of the infants in the control group developed anemia during the study. In the fortified group, about 15% of the infants were anemic at 12 months of age and 22% at 15 months, indicating that the product, used for only 6 to 9 months, could not control anemia in this very underprivileged group of infants.

Saarinen (11) used a proprietary infant formula containing 11 mg iron/liter as ferrous gluconate in 47 term Finnish infants, starting before 1 month of age and continuing the administration until 1 year of age. Cooked vegetables were started at 3.5 months, meat and eggs at 6 months, and table foods at 9 months of age. They also received an iron-fortified cereal (0.1 mg/g of dry cereal) starting at 5 months. Essentially none of these infants had any sign of iron deficiency during the first year of life as measured by hemoglobin concentration, transferrin saturation, mean corpuscular volume, or serum ferritin. In contrast, at 9 and 12 months of age, a low serum ferritin existed in about 15% of the 29 infants fed cow's milk and unfortified cereal.

There are very few studies of this nature in developing countries. In Chile, two different iron-fortified formulas have been the subject of investigations in recent years (24,25). Since a large program of free distribution of dry milk to infants or their lactating mothers exists in this country, covering 80% of the infantile population, it was thought that fortification of this milk with iron could reduce the high prevalence of iron deficiency. Under this program, 3 kg of dry milk are given each month from 0 to 6 months of age and 2 kg from 6 to 24 months of age. Mean duration of breast-feeding in Chile is about 3 months. Solids are usually introduced at 4 months of age.

The first fortified product was studied between 1972 and 1975. It was low-fat (12%) dry milk fortified with 15 mg elemental iron per 100 g of powder or 1 liter of reconstituted milk as ferrous sulphate. Geometric mean iron absorption from this formula in primarily iron-deficient infants was 3 to 4% (25). About 300 infants received the fortified milk from 3 months to 15 months of age. Controls received
the same milk without iron fortification. At the end of the trial, anemia had been reduced from 34.6% in the control group to 9.9% in infants known to be receiving fortified milk consistently. Differences in transferrin saturation and free erythrocyte protoporphyrin were small.

These results, although significant, were less than optimal due to the relatively low absorption of iron from this unmodified milk and to the fact that some of the product was consumed by other family members. The 0.3 to 0.4 mg of extra iron that was probably absorbed from the fortified milk was not enough to prevent iron deficiency in infants receiving no other fortified foods.

A second fortified formula was developed in the laboratory in 1975 as a result of studies demonstrating the importance of ascorbic acid on the bioavailability of fortification iron in milk (26). This was a full-fat (26%) dry milk fortified with 15 mg iron (as ferrous sulphate) and 100 mg of ascorbic acid per 100 g (1 liter of reconstituted formula). The product was slightly acidified in order to discourage consumption by other family members. Iron absorption from this milk in predominantly iron-deficient infants was 10 to 12% (24,25), 2.7 times higher than that from fortified milk without ascorbic acid given to the same infants (Fig. 1).

A pilot field trial was conducted with this formula between 1976 and 1978. The fortified milk was given from 3 to 15 months of age to 280 spontaneously weaned infants attending three National Health Service clinics in the city of Santiago. The regular unfortified full-fat dry milk powder was given to 278 infants. In both groups, eggs and fruits were given at 4 months, vegetables and meat soup at 5 months, unfortified cereals and legumes at 6 to 7 months, and regular table food

![FIG. 1. Absorption of fortification iron from two different milk formulas as compared in the same subjects by a double isotope technic. Infants received on day 1 low-fat milk fortified with ferrous sulphate and on day 2 acidified milk fortified with ferrous sulphate and ascorbic acid. (From Stekel et al., ref. 25.)](image-url)
at 9 to 12 months. Although these infants were of low socioeconomic condition, diarrhea was relatively uncommon and protein-calorie malnutrition affected less than 10% of the population.

The milk fortified with iron and ascorbic acid had a marked effect on iron nutrition, producing significant differences with the control group in all measured laboratory parameters at 9 and 15 months of age (Fig. 2). At 9 months, a hemoglobin concentration below 11 g/dl was present in 7.5% of the cases receiving fortified milk versus 34.7% in the control group. At 15 months, anemia existed in only 1.6% of the infants receiving the fortified product versus 27.8% of those

![Graph showing mean values of hemoglobin (Hgb), transferrin saturation (Sat), free erythrocyte protoporphyrin (FEP), and serum ferritin (SF) at 3, 9, and 15 months of age in infants receiving acidified milk fortified with iron and ascorbic acid (open circles) or unfortified milk (closed circles). Asterisks indicate that differences are significant at P < 0.001. (From Stekel et al., ref. 25.)](image-url)
receiving unfortified milk. Occurrence of anemia in the control group at 15 months would have been higher if cases with a hemoglobin concentration below 9 g/dl at 9 months had not been removed for treatment.

The same product was subsequently tested in a large regional field trial, under the normal operating conditions of the Chilean milk distribution program. At seven large clinics in the city of Santiago, infants born after 1 August 1978 received acidified milk fortified with iron and ascorbic acid after weaning; infants born before then received the regular unfortified program milk. The rest of the health care was identical in the two groups. A random sample of 400 infants born immediately before or immediately after the fortified milk was instituted was selected for detailed laboratory studies. Prevalence of anemia at 15 months of age was markedly reduced from 29.9% in the infants born in June/July to 5.5% in infants born in August/September. Enough iron was absorbed from the fortified formula to produce an increase in iron stores, as measured by serum ferritin (Fig. 3).

It is thus apparent that the use of adequately fortified milk formulas during the first year of life can prevent the development of iron deficiency in artificially fed infants. However, it must be emphasized that the iron bioavailability from these products may vary considerably. Ascorbic acid plays a critical role in this respect.

Iron-fortified cereals are also an effective and relatively inexpensive way of providing fortification iron to infants. They have the advantage that they can be

![Graph](image-url)

**FIG. 3.** Regional field trial of acidified milk fortified with iron and ascorbic acid. Cumulative frequency distribution of individual values of hemoglobin and serum ferritin at 15 months of age in infants born on June/July 1978 receiving unfortified milk (*broken line*) and on August/September 1978 receiving fortified milk (*solid line*). The height of the columns indicates the percentage of infants with hemoglobin <11 g/dl (*left*) and serum ferritin <10 μg/l (*right*) in each of the two groups.
used in both breast-fed and artificially fed infants. In the United States, especially prepared iron-fortified cereals for infants have been available for many years. For a long time, they were fortified with iron salts, such as sodium iron pyrophosphate, that are almost completely unavailable for absorption (27). This is probably why, despite their widespread use in infant feeding, they had little impact on the prevalence of iron deficiency (28).

The best demonstration of the effectiveness of fortified cereals in preventing iron deficiency in infants is the work by Moe (29). This author gave Norwegian infants from 3.5 months until 1 year of age a cereal fortified with ferrous saccharate at two different levels: 12.5 and 5 mg/100 g. As controls, he studied a group receiving an excessive amount of iron (more than 20 mg/day) in the form of fortified cereal plus oral medicinal iron and a group fed the regular Norwegian infant diet, which, at 12 months of age, provided a calculated daily iron intake of 3.4 to 7.0 mg. Infants given the 12.5 mg cereal had hemoglobin concentrations similar to those receiving more than 20 mg iron, whereas those receiving the 5-mg cereal had significantly lower values at 9 and 12 months. Anemia (Hb < 11.0 g/dl), which was very prevalent in the group receiving the unfortified diet (42.5% at 12 months), existed in 27.7% of the cases in the 5-mg cereal group but only in 4% of the infants in the 12.5-mg cereal group (Fig. 4). The author concluded that this cereal, fed regularly, twice a day from the age of 3.5 months, and providing a total daily dietary iron intake of about 10 mg at the age of 8 to 12 months, will produce an optimal hemoglobin concentration in almost all infants.

Dry cereals in the United States contain a much higher iron concentration (30). Since 1972, most of these products are fortified with reduced iron of small particle size. Two regular servings of 7 to 14 g/day of fortified dry cereal (45 mg iron/100 g of cereal) will provide 6 to 12 mg iron, of which about 4% is absorbed (31).

FIG. 4. Distribution of hemoglobin concentration at 1 year of age in infants receiving from the age of 2.5 months a cereal fortified with 12.5 mg iron/100 g (group B), the same cereal fortified with 5 mg iron/100 g (group C), and an intake of more than 20 mg iron/day in the form of fortified cereal plus oral medical iron (group A). Infants in group D received the regular diet with no extra iron (29). (From Dallman et al., ref. 24.)
This, according to the Committee on Nutrition of the American Academy of Pediatrics, is a sufficient supply of supplementary iron for most infants (16).

In areas of the world where breast-feeding is prolonged, cereals could represent a very good way of providing needed supplementary iron starting at about 4 to 6 months of age. At about the same age, infants that are exclusively breast-fed require calorie and protein supplementation. Cereals, fed as a gruel with a spoon, do not compete with suction from the breasts, thus contributing to the prolongation of breast-feeding.

Unfortunately, cereals traditionally used to supplement breast-fed infants in developing countries have several limitations: iron bioavailability is low, the quality of the protein is suboptimal, and the energy density is low when prepared as a gruel.

In our laboratory (E. Calvo, unpublished data) an extruded rice flour cereal fortified with 5% bovine hemoglobin concentrate has been prepared in an attempt to overcome some of these limitations. This cereal gives a suitable gruel preparation at 20% dilution and has an improved protein quality. It provides 14 mg of hemoglobin iron per 100 g with a mean absorption of the heme iron of 14.2%. It can be calculated that two servings a day of 20 g of this cereal will provide about 0.8 mg absorbed iron. The effectiveness of this product in prolonging breast-feeding and preventing iron deficiency is presently being investigated in a longitudinal field trial in Santiago.

Children

Theoretically, fortified milk and fortified cereals could also be used to provide extra iron to preschool children. In practice, however, preschool and older children must rely on the regular household diet. As already discussed, iron nutrition in these children will depend on the content and availability of iron from the different diets. Children will also benefit from iron fortification of products aimed at the general population.

In many countries, wheat flour is fortified with iron, thus increasing the iron intake from products such as bread and pasta. The impact of the consumption of fortified wheat flour on the iron nutrition of children has not been determined. The use of sugar fortified with sodium iron EDTA in the general population is presently under investigation in a large community study in Guatemala. This iron salt has special characteristics in its absorption behavior when mixed with food (32,33), which makes it a promising food fortificant. Preliminary results of the field studies seem to indicate a positive effect in children (F. E. Viteri, personal communication).

Common salt fortified with ferric orthophosphate and sodium acid sulphate (1 mg iron/g salt) has recently been tried in India as a means to provide extra iron to the general population (34). The product is reported to have good organoleptic characteristics and a good shelf-life. Large-scale field trials were conducted in three rural areas and one urban area located in different parts of India, each covering a
total population of 4,000 to 6,000. Hemoglobin levels were determined before and at 6, 12, and 18 months after the introduction of iron-fortified salt. Prevalence of anemia at the beginning of the trial was extremely high, particularly in the rural areas. In Calcutta, for example, 94.6% of the population was anemic. A highly significant increase in hemoglobin concentration occurred in all centers in essentially all age and sex groups. In Calcutta, at 12 months, hemoglobin had risen 3.3 g/dl in the 1- to 5-year-old group and about 3.2 g/dl in the 6- to 14-year-old group. Prevalence of anemia in the 1- to 5-year-old group (Hb <11 g/dl) was reduced from 96.3 to 38.8% in Calcutta, from 66.3 to 28.2% in Hyderabad, and from 19.1 to 9.1% in the urban center of Madras. Changes in the prevalence of anemia of a similar order of magnitude occurred in the 6- to 14-year-old group and also in essentially all other groups. The iron-fortified salt was acceptable to the population and its consumption was, reportedly, without any untoward effects.

Other products that are extensively used and provide extra iron to preschool children are the special food supplements supplied to developing countries by the Food for Peace Program of the U.S. Department of Agriculture. They include products such as corn-soya milk, corn-soya blend, wheat-soya blend, wheat protein concentrate blend, and whey-soya drink mix, all of which are fortified with iron, as ferrous fumarate, in the proportion of 15.6 mg iron/100 g. Iron absorption from these mixtures is quite low (35). However, based on their absorption studies, Morck et al. have calculated that when consumed in the recommended amounts, they can supply about half of the daily iron requirement of iron-deficient preschool children (35).

School lunch programs also provide an opportunity to supply extra iron to schoolchildren, where needed. In Chile, 6.7% of school-age children are anemic and 31.8% have a transferrin saturation below 15% (36).

The School Lunch Program in Chile includes, at breakfast or at tea time, three 10-g wheat flour cookies per child. The fortification of these cookies with a 6% bovine hemoglobin concentrate, resulting in a product with improved protein quality and good organoleptic characteristics and shelf-life has been proposed (J. A. Asenjo, unpublished data). Thirty grams of cookies provide about 5 mg of hemoglobin iron. Heme iron absorption from the cookies is about 20%, which should result in the absorption of 1 mg of iron per child on each school day. The effect of using these fortified cookies in the school lunch program is presently being measured in longitudinal studies in Santiago.

IRON SUPPLEMENTATION

When adequately fortified foods are not available, as is the case in many parts of the developing world, iron requirements in infants should be met by supplementation of the diet with medicinal iron.

Oral Iron

The effectiveness of oral supplementary iron in preventing iron deficiency was demonstrated a long time ago (37,38). Iron supplementation should start at about
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4 months of age in term infants and no later than 2 months in preterm infants, and should continue at least through the remainder of the first year of life. The Committee on Nutrition of the American Academy of Pediatrics recommends that the dose of supplementary iron should not exceed 1 mg/kg/day for term infants and 2 mg/kg/day for preterm infants, up to a maximum of 15 mg/day (16).

Ferrous sulphate is the standard preparation for oral iron supplementation. It is inexpensive and well absorbed. Several other soluble ferrous salts are equally well absorbed (39). Preparations containing other “hematinics” should be avoided. Ascorbic acid, which has a marked effect on the absorption of nonheme dietary iron, is probably not justified in combination with medicinal iron (40). Tolerance in infants is usually good. In one careful study, definite symptoms associated with preventive doses of oral iron were no different from those associated with placebo (41).

The main obstacle in achieving effective prevention with oral iron medication is compliance. The daily administration of a medicine to an apparently healthy infant for several months is very difficult to obtain, even from educated mothers. This is well exemplified by the work of Rios (personal communication) in our laboratory. He studied prospectively 130 preterm infants from birth until 1 year of age. At 3 months, oral iron supplementation, 2.5 mg/kg body weight, was prescribed to 65 of the infants who were receiving unfortified whole milk powder. The iron preparation, a commonly used liquid containing ferrous sulphate (FER-IN-SOL, Mead Johnson) was delivered every 3 weeks to each infant's house by a nurse who motivated the mother and checked for unused medicine. The other 65 infants received the same powdered milk fortified with 15 mg iron and 100 mg ascorbic acid per liter of reconstituted product. At 6, 9, and 12 months of age, hemoglobin concentration was significantly lower in infants on iron medication (Fig. 5). Anemia at 12 months existed in 23.9% of these subjects versus only 4.2% of those receiving fortified milk. The most likely explanation for the poorer results in the infants receiving medicinal iron was poor compliance, despite the very high motivation of the mothers and the careful supervision by professional personnel.

Parenteral Iron

In theory, parenteral iron is an attractive alternative for the prevention of iron deficiency in infancy. The full requirements for the first year of life can be administered in a single visit, avoiding the problems of interfered absorption of fortification iron by food and lack of compliance or intolerance to oral iron supplementation. It would be particularly useful as a preventive measure in situations where susceptible individuals are reached only sporadically by health services and are usually thereafter lost to follow-up.

Based on these types of considerations, we performed in 1975 a study in which 250 normal term newborns were given 150 mg of iron dextran (IMFERON, Fisons) intramuscularly before discharge from the hospital (M. Olivares, unpublished data). These infants were followed prospectively until 15 months of age. The results in
relation to prevention of iron deficiency were highly satisfactory. Only 1.3% of infants had a hemoglobin concentration below 11.0 g/dl at 15 months of age. Adverse reactions, occurring in 2.5% of the cases, were mild—skin rash, low-grade fever, and polypnea—in a 48-hr observation period. Other authors (42,43) have obtained similar results.

In 1977, Barry and Reeve (44) in New Zealand reported that parenteral administration of iron dextran was associated with an increase in the incidence of serious bacterial infections in the neonatal period. The study, however, was based on retrospective analysis of epidemiological data without controls run in parallel. A newer preparation of parenteral iron, iron-poly (sorbitol gluconic acid) complex, is claimed to have less adverse reactions than iron dextran (45). This product has not been studied in infancy.

Although further studies need to be carried out in order to clarify the issue of parenteral iron in the newborn, the possible risk of infection plus the possibility of severe anaphylactic reactions make its use, at present, unadvisable in young infants.

ACKNOWLEDGMENTS

The following investigators participated in the Chilean milk fortification studies: Mirna Amar, Marisol Cayazzo, Patricia Chadud, Gloria Heresi, Eva Hertrampf, Sandra Llaguno, Manuel Olivares, Fernando Pizarro, Ernesto Rios, and Tomás Walter. The expert secretarial help of Adriana Vargas is acknowledged.
This work was supported in part by grants from the United Nations University, The Consejo Nacional para la Alimentación y Nutrición (CONPAN), Chilean Ministry of Health, and the Departamento de Desarrollo de la Investigación, University of Chile.

REFERENCES


DISCUSSION

Dr. Siimes: I wonder why so much unsupplemented formulas are sold in areas where iron deficiency is common in infancy?

Dr. Fomon: In the United States, the major infant formula manufacturers produce formulas "with" or "without" iron, generally at the same price. Formulas "with" iron generally provide about 1.8 mg/100 kcal, whereas those "without" iron generally provide about 0.15 mg/100 kcal. Many physicians believe that the formulas with iron are responsible for adverse reactions—diarrhea, constipation, regurgitation, fussiness—and therefore prefer formulas without iron. There are few studies on this point. A study by Oski [Pediatrics 66:168,
1980] with 93 infants enrolled soon after birth and the majority studied until 6 weeks of age failed to detect any difference in manifestations between those fed formulas with and without iron. However, additional studies should be carried out.

'Dr. Hallberg: I think that in this important review, there should be a summary included on the findings you have made of diarrhea and infection in these two groups.

'Dr. Stekel: We have measured specific signs of gastrointestinal intolerance and especially diarrhea, and we have found that there is no increase in these in the group receiving the fortified formula, and that in certain periods of the summer there has been a significant decrease in the prevalence of diarrhea in the group receiving the fortified milk. There are some problems of interpretation because the fortified milk was acidified and the unfortified control was not, but at least we can say very clearly that there are no increased signs of intolerance.

'Dr. Dallman: There is another reason why the use of unfortified formulas has persisted. Pediatricians have justifiably tended to be very conservative about having formula constituents that deviate markedly from the composition of breast milk. Certainly, the iron-fortified products deviate markedly in respect to iron. As we have discussed, some deviation can be justified on the basis of the poorer bioavailability of iron from cow's milk formulas as compared to breast milk.

'Dr. Stekel: There is certainly a need for more documentation of the possible side effects of iron in formulas and, particularly, of medicinal iron. As I was reviewing material for my paper, I could find very few good studies. The one that I quote, which is the one by Burman [ref. 41], is probably one of the best ones—and I am not sure that the interpretation that I gave to the findings in that paper is really accurate. I said that the author found no important differences between infants given oral iron and the ones given placebo. Dr. Fomon commented the other day that if one looks carefully at the data there may be some differences. Side effects may be related to which iron preparation is given, or to the dosage. We know infants are often prescribed many times the recommended doses. These sort of things need to be studied.

'Dr. Finch: One possible cause of bowel symptoms may be a change in bacterial flora. It would be expected that an altered iron content might favor some bacteria over others. Is there any evidence relating to changes in bacterial flora in infants given high-level iron supplements or fortified formulas?

'Dr. Stekel: Not that I am aware of, and these studies are quite difficult to perform. We have done some studies on stool cultures, but these are probably not very relevant because we are studying the flora at a level of the gut where it is not really important. In order to sample the areas of the gut that need to be studied we need quite sophisticated techniques and I am not aware of any studies of this kind.

'Dr. DeMaeyer: Is there any information concerning the effect of repeated gastrointestinal infections on iron absorption, especially in young children.

'Dr. Chandra: The question of nutrient absorption in relation to diarrhea was discussed at a workshop in Bellagio recently. There was little information on iron or other minerals.

'Dr. Stekel: Isn't there information that even mild inflammatory states will impair iron absorption? I think this information is available.

'Dr. Cook: As I recall there was only one study published in the Lancet a number of years ago from Jamaica showing that fever impairs iron absorption in infants.

'Dr. Dallman: Another study by Bender-Götz and co-workers [Mschr Kinderheilk 124:305, 1976] came to the same conclusion. Iron absorption was decreased by about 50% in children with acute febrile infections but returned to control values after recovery from the fever.

'Dr. Guesry: I would like to return to the ascorbic acid question since Dr. Stekel has raised the point. The recommendation for ascorbic acid is 50 mg/day, but since you have shown that with a higher amount of ascorbic acid it is possible to increase the iron absorption, would you recommend increasing the level of ascorbic acid up to 100 or 200 mg?
Dr. Stekel: One is always hesitant to recommend the increase of a nutrient in a product based not only on a direct nutritional need for that nutrient, but, as it would be in this case, because of a pharmacological effect. However, knowing the wide safety range that we have with this particular vitamin, I have not hesitated to recommend in my country a concentration of 100 mg/liter.

Dr. Hallberg: I would like to comment on the suggestion of making several studies with different levels of iron fortification. Sometimes it is too easy to ask for more studies without considering the tremendous amount of work involved in making a good study. We need a few, but very good studies, designed so that interpolations can be made. It is not necessary to repeat studies in every country; there is then always a risk that confounding results are obtained because of poor experimental design, insufficient number of subjects, and so on.

Dr. Fomon: Although I agree that the number of clinical studies must be limited, I am not willing to retreat from my position that it is of considerable importance to determine whether fortification of an infant formula with ferrous sulfate at 0.9 mg/100 kcal (the calculated advisable intake) is as effective in achieving desirable iron nutritional status as the current fortification level of 1.8 mg/100 kcal.

Dr. Stekel: Coming back to the question of possible modifications of the intestinal flora, I wanted to ask Dr. Chandra if he thinks that some kind of information of this sort can be obtained from regular stool cultures, or if you really have to go into more sophisticated studies.

Dr. Chandra: Assessment of fecal flora is of limited value. Next best to the invasive procedure of duodenal aspiration, one may use the string test, which is employed for the diagnosis of Giardia infection.