Iron and Breast Milk

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The iron content of breast milk is often characterized as low. In fact, the amount of iron provided by breast milk appears to be adequate to prevent iron deficiency anemia for at least the first 6 months of life. However, if the same amount of iron is given in any food other than breast milk, this amount is inadequate and iron deficiency anemia does occur. Thus, iron in breast milk seems to be utilized by the infant to a unique extent. In addition, there is some evidence that the high degree of iron utilization in the breast-fed infant has a role in host defense mechanisms. A further understanding of the factors stimulating and limiting absorption of iron from breast milk, cow's milk, and proprietary formulas is needed in order to elucidate the mechanisms of iron absorption and metabolism as well as the role of iron on infections of the infant.

IRON CONTENT OF MILK

There appears to be a diurnal variation; morning milk contains less iron than milk in the evening (1). This led the investigators to the conclusion that the values in their initial study (2) were low due to the use of morning samples. During a single feeding, the foremilk has a lower iron concentration than the hindmilk, the range being from 0.3 to 1.0 μg/ml (3). Thus, like fat, the iron concentration of breast milk increases significantly during a single nursing. The concentration of iron in breast milk varies among women and in individual women during the lactation period, during the day, and during the nursing period. Thus, all these factors have to be considered when discussing the iron content of breast milk and the utilization of this iron. In contrast, the iron content of cow's milk or infant formulas is considered to be relatively constant compared to breast milk. Values for the total iron content of breast milk vary among laboratories where different analytical methods are used; less than optimal methods frequently yield unreasonably high values.

Recent studies usually give similar values for the iron concentration of breast milk, a range from 0.2 to 0.7 μg/ml, with colostrum values of 0.5 to 0.7 μg/ml declining to a mean value of around 0.2 to 0.4 μg/ml for mature milk (Table 1).

FACTORS AFFECTING BREAST-MILK IRON

It is not known if dietary iron or the iron status of the mother has any effect on the concentration of iron in breast milk. Some reports from India (4,5) indicate
that groups of nursing women having a high incidence of anemia have quite a high iron content in their breast milk; the values do not appear to be lower than normal. However, analytical problems may have contributed to these values. Murray et al. (6) did not find an effect of iron status of Nigerian women on breast-milk iron content. Neither iron deficiency (Hb < 10 g/dl) nor iron overload (Hb >12.0 g/dl; transferrin saturation > 60%) was found to affect breast-milk iron concentration. It should be noted, however, that the mothers in Murray et al.'s study cannot be classified as severely anemic. Whether a severe iron deficiency anemia, which is frequently observed in many developing countries, has any effect on breast-milk iron remains to be studied. Preliminary studies indicate that the milk of severely anemic (Hb < 8 g/dl) mothers in India has an iron concentration higher than the milk of control mothers (Hb >11 g/dl) (G.-B. Fransson, M. Gebre-Medhin, and K. N. Agarwal, personal communication).

Other studies also fail to find an effect of dietary iron intake on milk iron content (7,8). However, the range of maternal iron intake in these studies was not large, 15 to 40 mg/day. A very high dietary intake of iron, like that in Ethiopia where intakes are as high as 300 mg/day compared to normal intakes of 10 to 15 mg/day, does not appear to affect breast-milk iron; values were similar to those of Swedish women with corresponding lactation times (G.-B. Fransson and M. Gebre-Medhin, personal communication). Thus, the very limited data available do not indicate a correlation between maternal dietary iron intake or iron status and breast-milk iron.

It can be noted that when using iron supplements in the form of a water-soluble chelate of iron, nitrilotriacetic acid (NTA), it has been possible to increase the concentration of iron in the milk of an experimental animal (rat) and thereby to increase tissue iron levels of the suckling pups (9). Recently, it was also shown that, when a solid diet high in iron was given to rats, a similar effect on the milk iron was obtained (10). In addition, after feeding an iron-deficient diet, milk iron concentration and pup tissue iron was significantly decreased compared to controls. However, it should be noted that the increase in iron has only been observed in one species (rat) and at very high levels of supplementation. It does not follow that a similar effect could be obtained in humans. In fact, great caution should be exercised before doing any human experiments; conceivably, an increase in milk iron could have adverse effects (11).
IRON INTAKE

The daily iron intake of the exclusively breast-fed infant can be estimated by using the above values for breast-milk iron and data for 24-hr milk intakes of breast-fed infants. Such data have been obtained for Swedish infants (12) and American infants (13) and they show reasonable similarity, although there is wide individual variation. Mean daily intake varied from 673 ml at 1 month of lactation to 896 ml at 6 months of lactation, yielding a daily iron intake of 0.21 mg/day (0.044 mg/kg/day) at 1 month of age and 0.13 mg/day (0.017 mg/kg/day) at 6 months of age (Fig. 1). The daily iron intake data are similar or somewhat lower than those found in other recent studies (8,14). Official recommendations for iron intake have been given at 0.83 mg/kg/day (United States Food and Nutrition Board). However, as will be discussed below, these values are not directly applicable to breast milk because of differences in iron bioavailability, but serve as guidelines for infants not being breast-fed (15). The iron intake of an infant receiving the same volume of iron-supplemented cow's milk formula would be 4.0 to 10.8 mg/day (0.7-1.8 mg/kg/day), the nonsupplemented cow's milk formula 0.50 to 2.4 mg/day (0.13-0.37 mg/kg/day), and the soya formula, which is commonly supplemented, approximately 2.7 to 10.8 mg/day (0.5-1.9 mg/kg/day).

RECOMMENDATIONS ON IRON SUPPLEMENTATION

It has been estimated that the infant requires 0.5 to 0.8 mg/day of iron in order to prevent iron deficiency during the first year of life. This estimate is based on the fact that the infant is born with iron endowment of 75 mg/kg body weight and that 140 to 200 mg of iron must be absorbed during the first year to ensure iron sufficiency. By giving varying levels of iron to infants, it was shown that the highest level of hemoglobin was found in infants who received 1 mg/kg/day of iron (16). The Recommended Daily Allowance (RDA) is set at 10 mg/day and the maximum

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**FIG. 1.** Daily iron intake of infants (1-6 months).
level of supplementation recommended by the Committee on Nutrition of the American Academy of Pediatrics is 1 mg/kg/day for term infants and 2 mg/kg/day for preterm infants, up to a maximum of 15 mg/day.

In respect to infant formula, the absorption studies by Saarinen et al. (17) led to a suggested level of supplementation of 7 mg of iron as ferrous sulfate per liter. The recommendation of the American Academy of Pediatrics for iron-fortified infant formula is currently at least 6 mg of iron per liter (15). However, it should be noted that although the labeling on most iron-fortified infant formulas lists the iron content at approximately 12 mg/liter, the levels found in formulas vary considerably (18). In fact, some iron-fortified formulas contained as much as 40 to 60 mg/liter, whereas some unfortified formulas contained only 0.1 to 0.2 mg/liter. Whether the high values represent contamination caused by the production process, the container, or a mistake in the formulation is not known, but these high values (as well as the very low values) should be an area of concern.

The relationship between the mode of feeding and the incidence of iron deficiency anemia has attracted interest and is still under debate. Four breast-fed infants that had been exclusively breast-fed for 8 to 18 months had normal hematological values (19). In a subsequent larger study, exclusively breast-fed infants did not meet any criteria of iron deficiency at 6 months of age, whereas at 9 months 4% of the infants were judged as iron deficient (20). Infants fed a home-prepared formula based on cow's milk showed iron deficiency at 4 months of age; infants fed iron-supplemented formula did not show signs of iron deficiency during the first 12 months of life. Picciano and Deering (21) found similar hematological indices in infants fed breast milk and in those fed an iron-supplemented formula. In addition, Owen et al. (22) found no signs of iron deficiency in exclusively breast-fed infants at 5 months of age, although breast-fed infants had higher ferritin values when given supplemented iron. Woodruff et al. (23) found a high prevalence of low transferrin saturation in exclusively breast-fed infants at 6 months and 9 months, but according to other studies the criterion used for low transferrin might have been too stringent.

It has been argued that breast-fed infants should be supplemented with iron as ferrous sulfate at a level of 7 mg/day (24). This argument is based more on calculations of required iron supply during the first year of life than on an observed iron deficiency anemia. This recommendation has been questioned since any needs for supplemental iron would be very different in early infancy (when storage iron is still present) compared to late infancy. Furthermore, supplemented iron might bind to lactoferrin and thus inhibit the possible bacteriostatic role of this protein and increase the risk of infection (25).

The quantity of iron given is adequate to saturate lactoferrin completely and, as stated below, the lactoferrin-iron complex is very stable and stands both a lowering in pH and limited proteolysis without loss of binding capacity. It is possible, but not proven, that a bacteriostatic effect of lactoferrin may be exercised by lactoferrin in the gastrointestinal tract of the infant and that a dose of iron salt potentially could abolish this effect. It has been argued that a single dose of iron could not
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Iron in its water soluble forms, the ferrous (II) and the ferric (III) ions, is rarely found free in biological systems. These ions, of which the oxidized Fe\(^{3+}\) form is considerably more common, form complexes of varying natures, from simple complexes with anions such as phosphate and citrate to the intricate structure of metalloproteins such as transferrin and ferritin. Since the nature of these complexes has been suggested to affect the uptake of iron from milk and formulas, it is important to isolate and identify such complexes.

Milk has traditionally been regarded as composed of three major fractions: fat (lipid), casein, and whey. Conventionally, fat is removed by skimming (centrifugation) and the casein precipitated by addition of acid to a pH of 4.6. The whey is defined as the remainder from this process. In order to study the distribution of iron among, and within, the major fractions of milk, new and milder separation procedures have been introduced (26). The fat fraction can be solubilized into an outer fat globule membrane (OFGM), an inner fat globule membrane (IFGM), and a triglyceride (“core”) fraction. Since acid precipitation of casein causes changes in charges of proteins and therefore redistribution of iron, ultracentrifugation has been used to sediment casein micelles. The whey can be separated by ultrafiltration into a protein fraction and a fraction containing low-molecular-weight compounds such as salts and lactose. Subsequent to this separation procedure each fraction can be further analyzed by the use of gel filtration, ion-exchange chromatography, and electrophoresis.

The results of using this separation procedure on breast milk, cow’s milk, cow’s milk formulas (“humanized”), and soya formulas can be seen in Fig. 2 (B. Lönnnerdal and B. Sandström, unpublished data). (It should be noted that the whey fraction in soya formula is used to designate the fraction corresponding to the whey fraction of milk as described above.) A considerable proportion (33%) of the iron in breast milk is found in the fat fraction, whereas only 9% is found in the casein. The remainder, 58%, is consequently bound to compounds in the whey fraction.
In contrast, casein binds a larger proportion of iron in cow's milk (24%) as well as in the soya formula. The whey-adjusted cow's milk formula consequently contains less iron bound to the casein (28%) and relatively more iron bound to the whey (59%) than in cow's milk. The fat fraction contains 14% of the iron in cow's milk, whereas only minor proportions are bound to this fraction in the formulas, most likely due to the fact that this fat is derived from a mixture of vegetable oils presumably containing no iron.

The solubilization of the breast milk fat demonstrated that iron is predominantly bound to the outer fat globule membrane (64% of the iron in fat), whereas very little iron is found in the triglyceride fraction (Fig. 3). Preliminary experiments,
using gel filtration and gel electrophoresis, indicate that the major proportion of iron in the outer membrane is contained in xanthine oxidase (27). This flavine iron-molybdenum protein is known to be present in milk fat.

The iron bound to casein is believed to be electrostatically associated with negatively charged phosphoserine groups located in the casein subunits. Such a binding has been observed for iron in casein from cow’s milk (26) as well as for calcium (28). This may explain the very high proportion of iron bound to casein in cow’s milk. The casein content of cow’s milk is 8 to 10 times higher than that of breast milk. Consequently, cow’s milk formula also has a high proportion of casein-bound iron. Not much is known about the insoluble compounds binding iron in soya formulas, but possibly iron phytate can be part of this fraction.

The low molecular weight fraction, separated by ultrafiltration from the whey, contains 32% of the total amount of iron in the breast milk (55% of the whey iron). Corresponding values are 32, 21, and 2% for cow’s milk, cow’s milk formula, and soya formula, respectively. The nature of the low molecular weight complex(es) has not been determined, but the complex seems similar to a complex for zinc, which has been isolated and identified as zinc citrate (molecular weight 600) (29).

The whey proteins of breast milk have been separated by gel filtration and the major iron-binding protein has been identified as lactoferrin by immunoelectrophoresis (3). The peak for lactoferrin is very wide, most likely reflecting the tendency of this protein to form complexes with immunoglobulins. Transferrin is also present in breast milk; however, the concentration of this protein is very low (3) and the amount of iron bound to this protein is very small.

Lactoferrin is present in the milk of most species. The molecular weight of human lactoferrin is around 80,000 and the protein consists of one polypeptide chain. This protein has physical and chemical properties similar to those of transferrin; both proteins bind two ferric ions in the presence of bicarbonate ions. Even though both proteins bind iron strongly, transferrin releases its iron when the pH is lower than 4, whereas lactoferrin does not completely release its iron until the pH is 2 or lower (30). A remarkable property of lactoferrin is its comparatively high resistance to proteolytic degradation, especially in its iron-saturated form (31). This property has been believed to protect lactoferrin against proteolysis in the gastrointestinal tract of the infant.

Among the proteins in breast milk, lactoferrin is one of the major components. Concentrations of 1 to 2 mg/ml have been reported in mature milk (Fig. 4) (12); this constitutes around 10 to 30% of the total protein content. Higher lactoferrin concentrations have been reported in colostrum, consistent with the higher protein content of this fluid. The concentration of lactoferrin in human milk is unusually high in comparison to most species. For example, cow’s milk contains only 0.01 to 0.1 mg/ml of lactoferrin, and thus any formula based on cow’s milk will contain only minute amounts of lactoferrin. It is interesting to note that the concentration of lactoferrin in milk from both well-nourished and malnourished mothers in Ethiopia has been reported to be higher than in milk from well-nourished Swedish
It is possible that the iron status of the mother may affect the lactoferrin concentration, although as stated above there does not seem to be an effect of iron status on breast-milk iron concentration. The common Ethiopian diet provides unusually high intakes of iron compared to most other countries. If lactoferrin synthesis can be induced by high dietary iron while milk iron concentration is unchanged, this may be a mechanism for maintaining the bacteriostatic function of unsaturated lactoferrin.

Lactoferrin has been considered as the iron-binding protein in milk, yet, as stated above, there are other compounds in milk that bind iron. In fact, only 20 to 30% of the iron in breast milk is bound to lactoferrin, the remainder being distributed between fat globule membrane proteins, casein, and low molecular weight ligands. Thus, the degree of iron saturation of lactoferrin is exceptionally low, only 3 to 5% of its total capacity; this may prove to be important in its function. Earlier reports have given a higher degree of iron saturation for lactoferrin, between 10 to 30%. However, this is not possible, a fact which can be shown by calculating the total iron-binding capacity of lactoferrin, which is around 2.1 μg/ml. If the iron concentration of mature breast milk is 0.4 μg/ml and 25% of this iron is bound to lactoferrin, only 0.1 μg of the total capacity of 2.1 μg/ml can be occupied, which equals 4.8%.

The biological function of lactoferrin is not yet fully understood. There are data supporting a bacteriostatic role for lactoferrin in breast milk. Since the initial report by Bullen et al. (25) showed that lactoferrin can inhibit the growth of *Escherichia coli*, several studies have demonstrated that the growth of bacteria such as *Candida albicans*, *Streptococcus mutans*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, and *pyocyaneus* can be inhibited by lactoferrin in vitro (33). The bacteriostatic function of lactoferrin in milk is decreased by the addition of excess iron. This implies that unsaturated lactoferrin inhibits bacterial growth, and that it does so by its strong iron-sequestering capacity. With an exceptionally strong association constant for iron (\(K_{ass} = 10^{30}\)), lactoferrin can successfully compete with bacterial siderophores and thus inhibit proliferation and growth of bacteria. Although some in vivo studies support the results obtained in vitro, no studies have been done in human infants.
Some *in vitro* studies also show that lactoferrin may act in concert with secretory IgA, a specific type of antibody present in milk (34).

The fact that iron in human milk is very well absorbed by the infant has led to the suggestion that lactoferrin may promote the absorption of iron. The data available from experimental animals and humans are conflicting and will be discussed in detail in the next section. An interesting hypothesis has recently been proposed by Brock (35) in which the function of lactoferrin changes with age, and thus the degree of physiological maturation of the infant. In the newborn, iron absorption is poorly controlled, but high levels of lactoferrin in the milk and low gastrointestinal proteolytic activity tend to prevent iron from becoming available for absorption. As the infant grows older, the need for exogenous iron increases, milk lactoferrin levels decrease, and proteolytic activity increases, resulting in progressively more iron being released from lactoferrin and subsequently absorbed. Although intellectually challenging, the various facets of this hypothesis remain to be proven experimentally. The effect of lactoferrin on iron absorption will be discussed below.

**BIOAVAILABILITY OF IRON**

A difference in iron nutrition between breast-fed and artificially fed infants has been implicated for a long time. In 1928 MacKay (36) found that the hematological status of infants that had been exclusively breast-fed for the first 7 months was better than that of infants fed cow’s milk or formula. Although a lower incidence of anemia was observed or estimated in breast-fed infants compared to cow’s milk or formula-fed infants, it was not until 1954 that it was explained by the very high proportion (45–75%) of iron that is absorbed from breast milk (37,38). However, Feuillen’s study (37) was very limited (N = 2) and the tedious balance technique was used. Introduction of the use of radioisotopes allowed more sensitive measurements to be performed in infants, children, and adults. Schultz and Smith (39) showed, by using both extrinsic (adding the isotope *in vitro* to milk) and intrinsic (giving the isotope to the cow to have it incorporated into the synthesized milk) labeling, that about 10% of the iron in cow’s milk is absorbed. Cow’s milk actually inhibits the absorption of ferrous iron from a test dose while it has no effect on iron absorption from heme (40). The same authors also pointed out that the percentage of iron absorption decreases with the amount of iron provided. Therefore, only a small fraction (4%) of iron is absorbed from formula supplemented to a level of 12 mg/ml (41).

The first experiments to assess bioavailability of iron from breast milk by using radioisotopes were done by McMillan et al. (19) and Saarinen et al. (17). These two groups used different experimental designs but reached very similar conclusions. In the studies of McMillan et al. (19,42), adults were used and the incorporation of radioiron into red blood cells from extrinsically labeled human milk was measured after 2 weeks. A red blood cell incorporation of 20.8% was observed. The corresponding value for cow’s milk was 13.6%. The authors reason that red
blood cell iron incorporation corresponds to 80% of the total body iron uptake and thus 25% would have been absorbed. Making the assumption that iron absorption in infants is twice that of adults, the estimated level of absorption of breast-milk iron in infants is 50%, and that of cow’s milk 34%. Saarinen et al. (17) and Saarinen and Siimes (43) also used an extrinsic tag but measured whole body retention after 2 weeks in infants fed human milk, cow’s milk, and cow’s milk formula. These investigators found an iron absorption of 49% from breast milk, 10% from cow’s milk, and 7 to 9% from supplemented formula.

The contrast in the results obtained for iron absorption from cow’s milk between these two studies may be explained by a difference in digestive capacity between the adult and the infant. Although iron absorption in the infant may be twice that of the adult for a test dose of iron or an easily digested food, this may not be true for iron given in cow’s milk. Cow’s milk is very high in casein, almost 10 times higher than human milk, and it is known that casein in the stomach of an infant can form hard curds that can pass through the gastrointestinal tract without complete digestion. While there is very limited data on the human infant, we have recently observed in fasted suckling rats that 4 hr after a tube feeding of breast milk or cow’s milk the stomach of pups fed breast milk was virtually empty whereas that of pups given cow’s milk were full of white hard curd (44). Thus, cow’s milk may be well digested in the adult but only to a lesser extent in the infant, making the assumed factor of two incorrect. It is possible that the value for iron absorption from cow’s milk obtained by McMillan et al. (19), 17%, should not be doubled but rather corrected downward for less absorption of iron in infants fed cow’s milk. Therefore, a value closer to 10% obtained by Saarinen et al. (17) may be derived.

The finding of a high bioavailability of iron from breast milk led to the hypothesis that a factor(s) present in this milk promotes iron absorption. The high concentration of the iron-binding protein lactoferrin in breast milk and a significantly lower concentration in cow’s milk stimulated several studies on the role of lactoferrin in iron absorption. However, the results appear to be conflicting. McMillan et al. (42) demonstrated a decreased uptake of iron from a “simulated” human milk when iron-saturated lactoferrin was added. However, the iron content of the formula containing lactoferrin was three times higher than that of the formula without this protein, which may have affected the results considerably. Also, it is not described how the iron was added to lactoferrin and how much time was allowed to lapse between the addition of the iron and the consumption of the formula. By using everted duodenal sacks from rats and guinea pigs, DeLaey et al. (45) showed in vitro that human apo-lactoferrin (lactoferrin free from iron) inhibited mucosal transfer as well as serosal uptake of iron. Lactoferrin saturated with iron was not found to have any effect. In addition, when animals were given antibodies to lactoferrin, iron uptake increased significantly. DeVet and van Gool (46) found a negative correlation between the amount of duodenal lactoferrin and iron absorption in human adults. Both these groups suggested that lactoferrin may protect the intestinal mucosa from absorbing excessive amounts of iron by binding the iron in the intestine and thus making it unavailable to the infant. Iron uptake by lactoferrin
can, despite its very high association constant, be very slow and will be dependent on factors such as pH, presence of bicarbonate, and chelators. It has been shown that saturation of lactoferrin with iron as an inorganic salt (ferrous sulfate) is not complete at 24 hr. Thus, if iron saturation of lactoferrin is not analyzed, it is possible that iron is present in an inorganic form and may in fact become complexed by other compounds. That this may have occurred is also indicated by the exceedingly high iron to lactoferrin ratio in the lactoferrin preparation that was added to the formula, namely 200:1 instead of the stoichiometric 2:1 ratio. Therefore, a role for lactoferrin in iron absorption in human infants cannot be ruled out by the experiments of McMillan et al. (42).

In a series of studies, the bioavailability of lactoferrin-iron has been assessed in experimental animals. Absorption of iron bound to lactoferrin was similar to that from ferrous sulfate in weanling rats fed a purified diet (47). Using the suckling pig and a radioactive isotope of iron, uptake of iron into red blood cells and plasma was significantly faster from a milk formula supplemented with lactoferrin-iron than from the same formula with iron sulfate (48). Whole body retention after 7 days, however, was similar for both groups. Similarly, iron retention was the same for iron-adequate and iron-deficient weanling mice fed a milk diet. Apo-lactoferrin added to the iron-supplemented milk yielded values for tissue iron and hematological values similar to milk without lactoferrin, speaking against an inhibiting role for lactoferrin in iron absorption (49). It should be mentioned that in the above studies bovine lactoferrin was used. There are some data indicating that there may be a difference between heterologous and homologous lactoferrin (50). Thus, this possible species effect should be investigated even though the chemical properties of lactoferrin from different species appear to be very similar.

An enhancing role for lactoferrin (or another breast-milk component) in iron absorption from breast milk may be indicated from the study by Saarinen et al. (17). A tracer dose of radioiron appeared to be better absorbed when it was given with a meal of breast milk than when it was given alone to a fasted breast-fed infant, although the value for iron absorption in the fasted breast-fed infant was higher than for fasted infants fed cow’s milk. Others have suggested that iron absorption is “tuned” by homeostatic control to a level corresponding to the previous diet. Alternatively, as discussed previously, digestion of breast milk is considerably faster and the stomach in breast-fed infants is more likely to be empty than when cow’s milk is fed. In the case of cow’s milk feeding, a factor inhibiting iron absorption still may be present in the stomach when the tracer dose is given. In the infants fed cow’s milk, serum ferritin levels were lower than in the infants fed breast milk; this would lead one to expect a higher iron absorption in association with lower iron stores. The fact that this was not observed would support the existence of a hypothetical factor in cow’s milk inhibiting iron absorption in infants.

A developmental change in iron transport may be hypothesized for the breast-fed infants: as iron stores are depleted, more iron is absorbed and if the iron status of the body is still “suboptimal,” an even higher “gear” of homeostatic control may be exerted by the mucosal transfer system so that a developmental gradient of iron
absorption is created. While this reasoning is speculative, it would be interesting to study iron absorption at various ages. In contrast, Götze et al. (51) found increasing iron absorption with increasing age of the infant. It appears from the studies by Dauncey et al. (52) and Lundström and Siimes (53) that the premature infant has mechanisms controlling iron absorption that are quite different than the term infant. Consequently, it is evident that the preterm infant has other iron requirements and thus possibly a different efficiency of absorption of iron than term infants.

Lundström and Siimes (53) estimated that increase in total body iron in preterm infants (as inferred from hemoglobin and serum ferritin concentrations at 3 to 4 months of age) was similar in infants fed breast milk and a humanized (whey-adjusted) cow’s milk formula not supplemented with iron, whereas that of infants fed a home-prepared cow’s milk formula was considerably lower. This apparent contrast to term infants is hypothesized to be due to a difference in intestinal control of iron absorption in these infants allowing them to absorb similar amounts of iron, or to a lack of inhibition of iron absorption from any kind of milk in preterm infants. The lower iron gain of infants fed cow’s milk is believed to be due to increased intestinal loss of blood.

A necessary prerequisite for validating radioisotope iron absorption studies done with extrinsically labeled foods is that the results are similar to those that would be obtained with an intrinsic label, i.e., that isotope exchange is virtually complete. It was shown by Schultz and Smith (39) that extrinsically and intrinsically labeled cow’s milk iron was absorbed to the same extent. However, the intrinsic and extrinsic tags were studied in different subjects, which makes the results difficult to compare. Corresponding findings in adults were reported for a broader range of foods by Björn-Rasmussen et al. (54). Although the above studies indicate that isotope exchange occurs under many circumstances, it cannot be assumed a priori that this will be the case for breast milk. Recent data show that a tracer dose of radioiron will bind virtually exclusively to lactoferrin in human milk, whereas in cow’s milk the tracer will be distributed among the various fractions in a manner similar to that observed for native (“cold”) iron (55). Furthermore, it was shown that even after incubation of labeled breast milk with gastric juice aspirated from an infant, or lowering the pH to 3, lactoferrin was still binding the radioiron almost exclusively. Thus, it may be that isotope exchange is incomplete in the infant when a ligand with an unusually high binding constant for iron is present in an unsaturated form. If this is the case, it may be concluded that the previous studies on iron absorption using an extrinsic tag have been conducted on the lactoferrin-bound fraction of the iron in breast milk, i.e., approximately 30% of the total iron. The absorption of iron from other complexes may therefore not have been studied and may be different. Naturally, there is a possibility that redistribution of iron occurs in the gastrointestinal tract, so that iron bound to weaker ligands will be released and subsequently incorporated into lactoferrin. In the case that that would happen to the extent that virtually all iron in breast milk became bound to lactoferrin, the results obtained previously may be representative for the total pool of breast milk.
iron. Further studies are needed to elucidate the extent of isotope exchange and digestion of lactoferrin.

Another approach to estimate bioavailability of iron from various milk regimens has been suggested by Saarinen and Siimes (56). This method is based on estimating the increment in total body iron, expressed as the sum of hemoglobin iron and body storage iron, during specific times for which the intake of iron is known. However, although a reasonable estimate of the hemoglobin iron pool can be obtained, storage iron is admittedly more difficult to assess. These investigators used serum ferritin as a measure and attempted to correlate the logarithm of serum ferritin with storage iron (expressed as mg/kg body weight) based on values from adult males and females as well as newborn and young infants. The monthly increment in total body iron was found to be 20 mg for breast-fed infants, 6.5 mg for infants fed a home-prepared cow’s milk formula, and 33.5 mg for infants fed a humanized cow’s milk formula supplemented with iron (11 mg/liter). When these authors assumed a milk or formula intake of 1,000 ml/day at 2 to 4 months of age and an iron content of 0.7 mg/liter in cow’s milk and 1.0 mg/liter in breast milk, the comparative values as percentage retained of total intake were estimated at 70% for breast-milk iron, 30% for cow’s-milk iron, and 10% for the formula iron. The authors point out that monthly increments of total body iron were quite different after the age of 4 months when solid foods were introduced. Breast-fed infants did not gain any iron and formula-fed infants gained less than one-third of the iron gained in the previous months. In contrast, infants fed cow’s milk increased their total body iron more than earlier and considerably more than the breast-fed group.

Thus, the differences between the groups were of the same relative magnitude as those found by radioisotope studies. As pointed out by Saarinen and Siimes (56), these are not retention values and are not absolute figures because physiological loss of iron was ignored. In breast-fed infants this loss must be insignificant, whereas it is possible that occult blood loss was occurring in the infants fed cow’s milk.

The values obtained by the indirect method were considerably higher than those obtained by radioisotope studies. This may be explained by the fact that the infants in the isotope study were 6 months of age, whereas the infants in the total body iron increment study were 4 months of age. It was also speculated that a continuous supplementation with ascorbic acid may have increased the iron absorption values in the study using the indirect method.

Garry et al. (57) have recently used the approach of Saarinen and Siimes to estimate iron absorption from breast milk and formula with and without iron supplementation. In their study a correction was made for estimated daily loss of iron from skin, urine, and intestinal mucosa. From birth to 3 months of age, the increment of total body iron, for breast-fed infants (B) was 49 mg, whereas that of breast-fed infants supplemented with iron (B+) was 59 mg. Corresponding values for nonfortified formula (F) were 24 mg and for fortified formula (F+) 28 mg. Between 3 and 6 months the increments for the same four groups were −3 mg (B), 26 mg (B+), 7 mg (F), and 23 mg (F+). The percentage of iron intake
absorbed during the first three months of life was calculated to be 81, 10, 97, and 6%, respectively, and for the period 3 to 6 months, 10, 4, 22, and 3%, respectively. The data by Garry et al. (57) also suggest a high bioavailability of breast-milk iron, at least for the first 3 months of life. These investigators suggest that the iron content of human milk is insufficient between the ages of 3 to 6 months; the negative iron balance observed by the other investigators when solid food is given to breast-fed infants is not the cause in this study because the infants were exclusively breast-fed up to at least 5 months of age; however, body storage iron may shortly become depleted if exclusive breast-feeding is continued.

The method used in the studies by Saarinen and Siimes (56) and Garry et al. (57) has been questioned by Fomon (58). Using a more appropriate value for iron concentration of breast milk, 0.4 mg/ml, rather than the 1.0 μg/ml used by the previous investigators, he concludes that more than 100% of the iron in breast milk was absorbed. This appears to be correct, especially since the daily milk volume ingested by breast-fed infants is closer to 800 ml than 1,000 ml (as used in the calculated intake). It is pointed out by Fomon that the assumption that plasma concentration of ferritin bears the same relation to body storage iron in the infant as in the adult may be invalid. The approach of Saarinen and Siimes (56) must therefore be revised somewhat to yield more reasonable results. If one takes the two values from infants for serum ferritin and storage iron and makes this admittedly limited material into a linear function, a monthly total body increment of 5 mg instead of 20 mg may be obtained for breast-fed infants. With a daily intake of 800 ml of breast milk having an iron concentration of 0.4 μg/ml, 9.6 mg of iron will be fed monthly to a breast-fed infant. Thus, an absorptive value of 52% may be derived, very similar to that from radioisotope studies (49%). Therefore, with further information regarding the correlation between serum ferritin and storage iron in infancy, this approach may prove to be a valuable method.

**ADDITIONAL FACTORS AFFECTING THE BIOAVAILABILITY OF IRON**

In milk, as well as in other foods, there is a variety of factors enhancing or limiting the absorption of iron. Even with knowledge of the effects of the individual components, it is impossible to make predictions about the net result on iron absorption of all the components together. As shown previously, human studies clearly show a superior bioavailability of iron from breast milk as compared to cow's milk. Although a few factors (lactoferrin, casein) have been mentioned as examples, there are several differences between human milk, cow's milk and formulas that may be responsible for the differences observed.

The carbohydrate source has been shown to affect iron absorption (59). Lactose has a more stimulating effect than starch, which may be partially responsible for the lower bioavailability of iron from starch-based soya formula (60). Although both human and cow's milk contain lactose, breast milk contains 7 to 8% compared to 5% in cow's milk. It is not known whether such a difference will affect iron
absorption. The fat content and source have also been shown to affect iron bioavailability (59); however, considerably less is known about this area. It may be the fat content directly affecting iron absorption but it also may be the concomitant changes in carbohydrate and/or protein content. A low protein formula (15 g/liter) has been shown to enhance iron absorption compared to a high protein formula (24 g/liter) at the same level of iron supplementation (61). It is possible that a high content of casein will limit iron absorption by binding iron tightly. Thus, there could be a negative effect of a protein such as casein in cow’s milk and formula, while possibly a protein like lactoferrin could enhance iron absorption in breastfed infants; therefore, it is not necessarily the total protein content affecting iron absorption, but rather the composition of the protein.

There are several low molecular weight compounds affecting iron absorption from milks and formulas. Ascorbic acid is a known promoter of iron absorption, whereas phosphate is known to form insoluble iron complexes, thus limiting absorption. The phosphate content of cow’s milk is considerably higher than that of human milk, and most formulas are also higher in phosphate (62). In addition, other cations such as calcium, zinc, and manganese may interact with the absorption of iron. A high zinc-to-iron ratio has been shown to decrease iron absorption in rats (63). It is not known whether the commonly used zinc supplementation of formulas affects iron absorption. Likewise, it is not known if the manganese supplementation used in some formulas will affect iron absorption. However, it has been shown that iron supplementation at a modest level (6 mg/liter) significantly decreases manganese absorption in experimental animals (49), demonstrating an interaction between these two elements. The higher calcium content of cow’s milk and formulas compared to human milk may also affect iron bioavailability, either directly or indirectly, by potentially competing for the same promoters of absorption, such as lactose. A low content of copper in milk can precipitate a copper deficiency, which in severe cases can lead to anemia (64). However, this anemia is not caused by an effect on iron absorption but rather by a decrease in iron mobilization from the liver and the reticuloendothelial system caused by a reduction in the activity of ferroxidase, a copper-dependent enzyme. It is apparent that excess or deficiency of other elements will affect the iron status, even though our knowledge in this area is very limited.

Giving a solid diet (strained pears) in addition to a meal of breast milk has been shown to decrease iron absorption in adults (65). In addition, Saarinen and Siimes (56) showed a marked drop in monthly total body iron increments shortly after solid foods (vegetables, fruits) were introduced. This decrease was noticed in both breast-fed and formula-fed infants. Evidently, the effects of mixed diets on iron absorption should be investigated further.

The fecal flora of breast-fed infants is quite different from that of artificially fed infants. Whereas breast-fed infants are primarily colonized with *Lactobacilli*, formula-fed infants have mostly coliform bacteria (62). The *Lactobacilli* produces a lower intestinal pH (approximately 5) than the *E. coli* (approximately 7), thus facilitating iron absorption. It is known that iron absorption is increased with lower
pH. In addition, cow's milk has a higher buffering capacity compared to human milk. Thus, the stomach content will be relatively more acidic in breast-fed infants than in infants fed cow's milk, again favoring iron absorption from breast milk. Another factor that should be considered is the effect of hormones on the gastrointestinal physiology. It has recently been shown that human milk, but not cow's milk, is high in concentration of a peptide similar to epidermal growth factor (EGF) (66). This peptide hormone has been shown to decrease gut acid secretion and also to stimulate growth and proliferation of intestinal mucosal cells, which may be envisioned to enhance iron absorption. Prostaglandins may also affect acid balance as well as intestinal mucosal transfer.

**IRON, BREAST MILK, AND HOST RESISTANCE**

The effect of iron status on host resistance has attracted considerable attention. As pointed out recently, several of these studies have been retrospective, and infection was not directly confirmed or characterized; therefore, criticism with regard to the control groups can be raised (67). In the past, iron deficiency was believed to increase the incidence of infection; however, there currently are studies with results to the contrary. Some studies show either no effect of iron deficiency or a lower incidence of infection with iron deficiency. A defect in the cell-mediated immune response has been documented in iron deficiency, but the overall effect of iron deficiency on host defense mechanisms in infants remains to be studied in carefully controlled prospective studies. In contrast, iron overload or iron supplementation in humans has also been implicated to have an effect on the incidence of infection. High doses of iron are postulated to result in a high degree of saturation of transferrin. Serum \textit{in vitro} has been shown to inhibit growth of some bacteria; this effect can be abolished by the addition of iron. This presumed function of unsaturated transferrin and its inhibition is thus similar to what has been previously described for lactoferrin. Some support for the theory of a harmful effect of iron supplementation has been gained by the study of Murray et al. (6) in which the iron supplementation of iron deficient subjects appeared to be related to a reactivation of malaria.

The relationship between iron status, mode of feeding, and incidence of infection is even more uncertain (68). As mentioned previously, a low incidence of infection in infants has been ascribed to breast-feeding; it has been hypothesized that lactoferrin may, at least in part, be responsible for this protective effect. The low concentration of iron in breast milk and the rapid uptake of iron by mucosal cells, together with an unsaturated (still functional) lactoferrin in high concentration, would be prerequisite for such an effect. Although the two former prerequisites have been established, the latter prerequisite, high concentrations of unsaturated lactoferrin in the gastrointestinal tract, needs confirmation. Other antibacterial and antiviral factors in breast milk such as secretory IgA, lysozyme, and mono-laurylrate should also be considered in connection to lactoferrin and investigated. It has been shown that the bacteriostatic property of breast milk can be inhibited or destroyed.
by the addition of iron or by boiling; however, this does not prove that lactoferrin saturation was directly affected nor that the effect of lactoferrin was destroyed by boiling (34). Until the questions about lactoferrin bacteriostatic function \textit{in vivo} have been resolved, it seems reasonable to avoid iron supplementation of breast-fed infants since, as stated before, iron status of exclusively breast-fed infants appears to be adequate (15,68).

In the case of formula-feeding, it is evident that iron supplementation should be used in order to prevent iron deficiency anemia. Since lactoferrin is present in very low concentrations or absent in formulas, the supplemental iron would have little effect on any possible bacteriostatic mechanisms provided by lactoferrin in the intestine. It has been shown \textit{in vitro} that varying the iron content of formula from 0 to 12 g/liter did not affect the formula's ability to sustain bacterial growth of \textit{E. coli} (69). In addition, it has been argued that the increased amount of iron absorbed from supplemented formula will have little effect on transferrin saturation in serum, thus making it unlikely that there would be a systemic effect (68). However, it is not necessary that supplemented iron that is needed would counteract a potential beneficial effect of minimized iron accessibility to bacteria. It has been suggested that iron bound to lactoferrin may be a valuable form of iron supplementation (48,70). Although lactoferrin is a minor component of bovine whey, it is quite possible to purify or concentrate this protein in large quantities from this source. Whey is a major by-product of cheese manufacturing; the huge quantities produced are considered more as a waste problem than a source of nutrients, primarily because of its low protein and high lactose content. It is possible that partially saturated lactoferrin can be used as a supplement, providing both a source of iron and as a protection against infection. Although iron from lactoferrin appears to be highly available, further research is clearly needed to show if this hypothesis of using lactoferrin in infant formulas is viable.

**CONCLUDING REMARKS**

It is evident that iron in breast milk has a very high bioavailability and that term breast-fed infants do not need iron supplements for the first 6 months of life. The mechanisms responsible for this high bioavailability are not known; however, at least part of the difference in bioavailability between human milk, cow's milk, and formulas may be explained by the difference in content of factors enhancing binding and iron absorption. Further studies on the role of lactoferrin in breast milk will give information about the role of this protein in iron absorption and host defense mechanisms. Other factors to be considered with regard to iron bioavailability are growth factors, intestinal pH, and microflora. With increased knowledge about factors promoting iron absorption in breast-fed infants, it may be possible to design formulas with improved iron bioavailability to be used when mothers cannot successfully nurse their infants.
REFERENCES


DISCUSSION

Dr. Stekel: May I ask you for a first comment: how would you summarize your view of the way that iron is absorbed from breast milk? Why is it absorbed as well as we think it is?

Dr. Lönnrdal: I think that you have to take it as an educated guess. I think that the lactoferrin iron is highly available. I think it will be taken up by the infant—to what extent I don’t know—but I certainly do not believe in an inhibitory effect of lactoferrin on iron absorption. I think that the low molecular weight iron, if being in the low molecular weight form or by that time taken up by lactoferrin, also represents an available pool of iron. It is possible that the flavin part of the xanthine oxidase molecule in the fat also could be available. So, I think that we have potentially three promoters of iron absorption in the breast milk, whereas we have a relative lack of inhibitors of iron absorption. We have very little casein; the casein that is there is very easily digested. I think it is very interesting that if you do intubation studies in suckling rat pups and give human milk, formula, and cow’s milk, and open the pups after various time periods, it is amazing how fast and well the human milk is cleared compared with the cow’s milk and the formulas, in which you see
a cheesy rubbery clot both in the stomach and in the upper part of the intestine. I think this would be the case for human milk: relative abundance of promoters and the relative lack of inhibitors of iron absorption, such as calcium, phosphate, and casein.

Dr. Fomon: If lactoferrin iron is available, do you speculate that it became available through digestion of the lactoferrin molecule? If so, the molecule would presumably not reach the colon where it is believed to interfere with bacterial growth.

Dr. Lönnerdal: I think that the lactoferrin molecule would be undegraded to a large extent. I think that there are receptor sites in the small intestine, which facilitate the uptake of iron because of a very strong binding constant. The receptor site possibly could take care of that. The abundance of intact, or at least immunologically intact, lactoferrin in the feces would support that. I have quantitative determination of lactoferrin per g feces. We made an extract and ran immunoelectrophoresis, but I don't have the amount of feces produced by the infant. So I don't have any balance figures, but I was amazed that on doing a fairly diluted extract from the feces and just doing immunoelectrophoresis there was a high concentration of lactoferrin.

Dr. Fomon: What is your final conclusion about the percentage of human milk iron in lactoferrin?

Dr. Lönnerdal: Twenty-five percent.

Dr. Dallman: I have two related questions. First, is there any evidence that the lactoferrin might be binding other metals. The other question is whether you have tried any experiments under conditions that simulate digestion to see if there are any shifts in the iron distribution as the milk is subjected to pH changes and other conditions that correspond to the stomach and upper duodenum.

Dr. Lönnerdal: For the first question, I think that lactoferrin is present in a very unsaturated form. We recently found that virtually all the manganese in human milk is bound to lactoferrin, but there is so little manganese. About 2 to 5% of the binding capacity of lactoferrin is utilized by iron. We don't find any zinc bound to lactoferrin and we don't find any copper. Even if you can force copper or zinc on lactoferrin in vitro, we don't find anything there in vivo. Concerning the second question, we don't have any results yet, but we are at present digesting milk, both in vivo and in vitro, to study what is happening with the distribution among the compartments.

Dr. Hallberg: Is there really a need for iron in the full-term infant during the first 6 months? Has nature designed the composition of the breast milk in such a way that it should be a good source of iron—or is it possible that the very small amount of iron in the breast milk has other biological functions not related to the iron status of the baby?

Dr. Lönnerdal: We are not sure what the physiological importance of some of these sources of iron in the breast milk is, but I still think that the low quantity of iron that the infant gets from breast milk is important if you look at the data of Dr. Siimes. If an infant is given a nonfortified cow's milk formula, for example, instead of breast milk, you see signs of iron deficiency anemia quite early, even at 4 months.

Dr. Cook: Lactoferrin is a fairly strong iron chelate. I wonder then why iron saturation of lactoferrin is so low in milk and why only 10 to 20% of the iron in milk is bound to that protein.

Dr. Lönnerdal: I think that the iron within the flavin compartment of xanthineoxidase is not easily exchangeable with the lactoferrin; even if the lactoferrin has such a strong binding constant it does not get through to it. With regard to the low molecular weight iron, we also have to consider that binding is the product of the binding constant and the concentration of the ligand. Take, for example, citrate: you have a concentration of 1 mM in the breast milk, which is a high concentration if you compare it to the molar concentration of lactoferrin. You always have to calculate the equilibrium between those compartments and that may be the reason why you will see part of iron bound to citrate.
Dr. Cook: Another explanation may be the pH effect. Perhaps there is a major shift in lactoferrin binding after ingestion of the milk at a lower pH. Perhaps a much higher proportion of iron is taken up by lactoferrin at the lower pH of the gastric content.

Dr. Lönn erdal: That is quite possible because the binding of, for example, citrate iron will rapidly decrease with pH, much more than for lactoferrin.

Dr. Garby: Is lactoferrin from one species the same as lactoferrin from another species?

Dr. Lönn erdal: They are very similar, that is, they crossreact immunologically, but they seem to have slightly different physiological activity. There are very few comparative studies that have been done and they seem to show that the homologous form for the species will be more efficient than the heterologous form and, of course, in these studies that I refer to, we used bovine lactoferrin because we used such large quantities. When we do these studies in the human we will use human lactoferrin and we will compare it with bovine lactoferrin.

Dr. Fomon: If in the gastrointestinal tract there are receptors that remove iron from the lactoferrin, it would seem important to know the quantitative aspects of this process. One might imagine that the addition of iron to human milk would result in greater saturation of the lactoferrin and, therefore, a larger amount of iron to feed to the receptors.

Dr. Lönn erdal: It is a possibility.

Dr. Cook: Another possibility might be that there is a specific receptor for lactoferrin or that the iron-lactoferrin complex actually enters the cell. Dr. Huebers has suggested that the transferrin may facilitate iron absorption by its secretion into the gastrointestinal lumen and its reentry with iron into the mucosal cell. Perhaps lactoferrin also enters the mucosal cell and is a species-specific phenomenon in that bovine lactoferrin would not enter the human mucosal cell. I wonder if you care to speculate on that, Dr. Finch?

Dr. Finch: We have done some studies involving lactoferrin but our work is so limited that I hesitate to comment. We did bind iron to lactoferrin derived from human milk and fed this to adults. Absorption of iron was markedly reduced as compared to the absorption of an iron salt. Other studies have involved gut loops in rats. There we have used human lactoferrin which may negate physiological interpretation. However, in this instance also, there was a marked reduction in absorption. Thus, we have been unable to demonstrate any positive role of lactoferrin in iron absorption.

Dr. Siimes: My comment relates to Dr. Lönn erdal's concern about the deficiencies of other minerals. There are very few data up to now that have any real clinical significance in this regard, but my concern relates to the excessive intake of other minerals in the presence of marginal iron intake, especially since there are no recommendations even for industrially made formulas.

Dr. Fomon: What is your speculation about the percentage of the iron in the whey-protein fraction associated with proteins other than lactoferrin?

Dr. Lönn erdal: I would say that a very small proportion of iron could be bound to other proteins than lactoferrin: it is virtually exclusively lactoferrin.

Dr. Stekel: It has been traditionally believed that the iron concentration in breast milk has little to do with the iron nutrition of the mother. Do you think that what you would have to do would be to raise the levels of serum iron as the mother is secreting milk and that this is what you are really changing with your oral iron supplementation?

Dr. Lönn erdal: I think it is very difficult to speculate, especially in the light of the most recent reports mentioned in the paper, in which it was found in India in severely anemic mothers that both lactoferrin and iron was higher than in the milk of nonanemic mothers. One could formulate a lot of nice hypotheses, but we don’t have much evidence.

Dr. Hallberg: I would like to come back again to my first question, because I am not quite satisfied. What good data do we actually have about the total amount of iron in the body at 6 months in relation to the total amount of iron at birth; how much extra iron needs to be absorbed during that period of time to cover the growth and to cover the losses? How much extra iron do we need; what do we know about it?
Dr. Fomon: The best data on iron content at birth are those of Southgate, Hey, and Widdowson (unpublished data) from whole-body analyses of stillborn infants or of infants who died soon after birth. The iron content of an infant with a birth weight of 3.0 kg is about 227 mg (85 mg iron/kg of fat-free body mass) and that of an infant with a birth weight of 3.5 kg is about 268 mg (90 mg iron/kg). I am reasonably confident about data on iron content at birth. At 6 months of age, there are no satisfactory data, but I think it is possible to make a reasonable estimate by a factorial approach. Most of the iron will be in the circulating red cell mass and this quantity can be estimated on the basis of available data. Next, an estimate of muscle mass can be made and, from this, an estimate of iron in the form of myoglobin. Finally, an estimate of storage iron must be made and this is the most difficult. However, in the 6-month-old infant, storage iron will account for a small percentage of total body iron so that a relatively large percentage error in estimating quantity of storage iron will result in only a small error in the estimate of total body iron. It is not very good, but it is the best we can do at present.

Dr. Stekel: I would like to show some calculations. According to these calculations a relatively small increase in total body iron would be expected between birth and 6 months of age on the average, and maybe even the little amount of iron that can be absorbed from breast milk would be enough.

Dr. Hallberg: How much iron is in store at that time?

Dr. Dallman: We may not know very much about iron in terms of total body composition data, but we do have information on serum ferritin in infants that allow some inferences about storage iron. In term infants, iron stores become marginal at about 4 to 6 months of age, especially with cow’s milk formulas that are unfortified with iron.

Dr. Siitnes: In my mind, this is fairly clear. However, in some individuals there is quite a large need of iron even during the first 6 months, in particular if they are exclusively on breast milk because the concentration of iron in breast milk is very variable. The infant cannot determine the concentration. Secondly, the infant’s individual hemoglobin mass at birth and at 6 months of age is quite variable. Thirdly, the growth rate (iron need) varies.

Dr. Stekel: Studies that compare iron nutrition status of breast-fed infants and infants that are fed unfortified cow’s milk show very clearly that at 6 months of age there are differences between the groups as measured by various laboratory parameters. This could be due to the increased iron absorption from breast milk, to smaller iron losses, or to the facilitating effect of breast milk on iron availability from the rest of the food that the infant is taking. I think this discussion has been very interesting, but we should make clear that this group is not really doubting that breast-milk-fed infants during the first 6 months of age have an advantage in iron nutrition over artificially fed infants not receiving fortified foods.

Dr. Hallberg: I would also like to ask Dr. Lönneldal about the different composition of milks in different species. Does that have anything to do with differences in iron nutrition or is it mainly explained by differences in requirements for energy, proteins, and so on for different rates of growth? Do you think that nature’s design of milks has taken into account a good iron nutrition? Can we learn anything about the importance of the iron in milk from studies on other species?

Dr. Lönneldal: I think that I can agree to the extent that the overall composition of milk is more important in reflecting the requirements for growth; I don’t think the primary concern is iron.