HUMAN iron requirements and metabolism of iron during the first 18 months of life have been the subjects of a number of reports, reviews, and commentaries over the past decade. Sufficient knowledge has been accumulated to permit a clear statement of dietary recommendations. Implementation of these would assure a satisfactory iron intake for the majority of North American infants and minimize the incidence of serious iron deficiency.

Several official recommendations concerning human iron requirements have been made. Not all have emphasized clearly the unique requirements of infants, especially low birth weight infants. In addition, they have failed to agree upon dietary requirements during the first year of life and have not indicated practical ways of achieving a satisfactory iron intake. The present memorandum reviews current knowledge concerning iron needs of infants, attempts to quantitate iron requirements in relation to birth weight and age, and examines practical methods for assuring adequate iron intakes. In addition, certain persistent gaps in our understanding of iron metabolism, subjects of controversy, and areas of investigative potential are reviewed.

IRON ENDOWMENT OF THE NEWBORN

Data obtained from carcass analysis performed on a small number of stillborn infants indicate that the body of the average term weight infant contains about 75 mg/kg of iron. There is a considerable range, however, in the actual values obtained by this measurement. The iron content of the circulating blood can be fairly accurately estimated from the red cell mass, and it is evident that more than three quarters of the infant's iron endowment is in the red cell. Tissue stores as such probably account for less than 10 to 20 mg of iron. No data are available concerning the effect of maternal iron depletion upon the extra-hemoglobin iron stores of the fetus; but, because of the small size of this iron compartment, its effect on iron endowment must be minimal. Since iron stores cannot be measured accurately in living infants, most attention has centered upon those factors which influence the initial hemoglobin mass. In normal newborns, levels of hemoglobin in cord blood vary from 13.7 to 20.1 gm/100 ml and hematocrits vary from 53% to 79%. Differences between these extremes may constitute differences in body iron amounting to as much as 50 mg. The factors which contribute to this variability are not well defined. Most evidence indicates that the maternal iron status has little effect on the infant's initial hemoglobin level. Multiparity, low socioeconomic status, and racial factors are commonly linked with a high incidence of iron-deficiency anemia in the older infant. The frequent association of these situations with low birth weight and with an inadequate postnatal intake of iron are probably far more important than any maternal effects on the infant's iron endowment. Likewise, the magnitude of the placental transfusion, although important, does not have the decisive effect upon a broad range of neonatal hemoglobin values. A systematic study of the regulation of fetal erythropoiesis is needed to provide a better understanding of the causes of variability in the infant's iron endowment.

During the 6 to 8 weeks following birth, erythropoiesis virtually ceases. The concentration of circulating hemoglobin decreases at a rate which is proportional to the short life span of fetal red cells and to the expanding volume of distribution. The iron derived from red cell breakdown is retained and used when hematopoiesis resumes. The

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size of this reserve and the time and rate at which it is utilized depends upon the size of the initial hemoglobin mass.

In addition to low birth weight infants and those with low initial hemoglobin levels, infants who experience various types of blood loss are at risk for development of iron deficiency. The iron endowment of an occasional infant may be reduced by blood loss in the perinatal period. Massive fetomaternal hemorrhages during pregnancy, though unusual, have been documented and iron-deficiency anemia due to chronic transplacental hemorrhage has been recognized at birth. Transfusions between identical twins, energetic diagnostic phlebotomy, external hemorrhage, and exchange transfusions may significantly diminish the hemoglobin mass.

The only practical indicators of the newborn's iron endowment are body weight and initial hemoglobin level. Measurement of hemoglobin or hematocrit should be performed in all infants in the neonatal period if an assessment of iron endowment is sought. This may be performed from free flowing capillary blood on the third or fourth day of life. When this value is examined in relation to birth weight, most infants with greater than normal iron requirements during the first year will be identified.

ASSESSMENT OF IRON STATUS OF THE INFANT

A well defined sequence of changes occurs in progressive iron depletion.

1. The storage forms of iron, hemosiderin and ferritin, disappear and cannot be demonstrated in bone marrow and other reticuloendothelial tissues.

2. The level of serum iron decreases and concomitantly the serum iron-binding capacity increases, resulting in a decreased percent iron saturation. A serum iron saturation of less than 15% is indicative of iron depletion.

3. A slight decrease in the circulating red cell mass occurs.

4. Changes in red cell morphology, including microcytosis and hypochromia, and poikilocytosis appear.

5. Anemia of a progressive degree of severity supervenes.

6. Decreases of the intracellular iron content of enzymes ultimately develop, although the point at which this depletion begins is uncertain.

During infancy, normal values for the various measures of iron balance differ considerably from those observed in adults. Unless appropriate standards based upon age are used when evaluating infants in the first 18 months of life, misinterpretations are unavoidable. Bone marrow hemosiderin, a form of storage iron that is easily accessible to study, is virtually absent after 6 months of age. Levels of serum iron in healthy infants are lower than those of adults. The ranges of hemoglobin and hematocrit values are considerably lower than those of the adult. The practice of reporting hemoglobin values of infants as a percent of an arbitrary adult standard should be abandoned to avoid an unwarranted diagnosis of anemia.

Hemoglobin concentration and hematocrit are widely used to assess iron adequacy. Sturgeon reported that, when normal infants were provided with relatively generous amounts of food or medicinal iron (between 1 to 2 mg/kg/day), the mean hemoglobin level at 1 year of age was 11.6 gm/100 ml. Administration of parenteral iron to such infants at 9 months of age increased the mean hemoglobin by less than 1 gm/100 ml (mean, 12.3 gm/100 ml). Between 3 and 18 months of age, a hemoglobin of about 12 gm/100 ml, or a hematocrit of 36%, may be considered optimal. Since hemoglobin and hematocrit values will assume a "normal" or Gaussian distribution, hemoglobin levels as low as 11 gm/100 ml, and hematocrits as low as 33% will fall within one and a half standard deviations of these means and should be considered "normal."

The prevalence of iron depletion or iron deficiency depend upon the criteria employed for diagnosis. By the time significant
degrees of anemia develop due to inadequate hemoglobin synthesis, iron deficiency is fairly advanced and morphologic abnormalities of the red cells are evident. The need to fulfill at least minimum diagnostic criteria for iron deficiency anemia must be emphasized. Minimum criteria include microcytosis and hypochromia of the red cells in a smear of peripheral blood and a response to specific therapy. A careful history (including family history), physical examination, and examination of the blood smear may suggest other forms of anemia, for which iron therapy will be ineffectual.

NON-HEMOGLOBIN ASPECTS OF IRON DEFICIENCY

Iron is an important constituent of several intracellular oxidative enzymes. The activities of various iron-containing enzymes have been studied in iron-deficient animals and humans. Activity of some enzymes, and cofactors such as cytochrome C and aconitase, is decreased while activity of others, such as catalase and cytochrome oxidase, is unchanged. Whether or not these decreases have functional significance is uncertain. For example, the respiration of leukocytes from iron-deficient patients is normal and oxygen consumption by the iron-deficient patient does not differ from normal. On the other hand, oxidative metabolism in muscle homogenates from severely iron-deficient rats is significantly impaired.

An increase in the frequency of respiratory infections has been reported in infants with iron deficiency, as well as a reduced incidence in such infections in children receiving iron supplements, even when significant anemia was absent. Confirmation of such effects would imply previously unsuspected metabolic functions of iron in humans. The proper design and control of prospective studies to document this observation are extremely difficult and, at present, such effects of iron deficiency or of therapy must be considered unproved. Symptoms such as fatigue, weakness, and pallor, commonly ascribed to iron deficiency, have been shown to be unrelated to the levels of hemoglobin and hematocrit in surveys of otherwise healthy individuals. The entire question of tissue effects of iron depletion is of great interest and demands imaginative investigation.

IRON ABSORPTION

Iron is absorbed from both dietary and medicinal sources even early in life. However, in the term infant, only a relatively small amount of absorbed iron is incorporated into circulating hemoglobin during the first 6 months of life. This point was demonstrated convincingly by the studies of Smith and associates, who labeled the hemoglobin of infants in utero with Fe. By 6 months of age, the specific activity of the hemoglobin had decreased by only about 20%. These data indicate that only a small amount of postnatally absorbed iron is incorporated into hemoglobin and support the observations that iron supplementation of the diets of full-term infants has a minimal effect on hemoglobin levels during the first 4 to 5 months of life. Iron which is absorbed in the early weeks of life, however, may exert a prophylactic effect against iron deficiency anemia in the later months of infancy. By contrast, premature infants incorporate considerable amounts of dietary iron into hemoglobin by 2 to 4 months of age.

The efficiency of absorption of various forms of dietary iron depends to some extent upon the food in which it is contained. In most estimates of dietary iron requirements, an absorption of 10% is assumed. This value is merely a convenient approximation and may not be valid for an individual patient. Non-anemic infants may absorb between 5 and 20% of iron from eggs, meats, and cereals. In contrast, premature infants have been shown to absorb an average of 32% of iron contained in fortified milks. This is comparable to absorption of medicinal iron by infants with iron deficiency.

Dietary constituents such as ascorbic acid increase absorption of dietary iron ap-
parently by maintaining ionic iron in the ferrous form. Other substances such as phosphates and phytates may decrease iron absorption by forming insoluble complexes, although the effect of phytates present in the usual diet is probably not significant.

IRON EXCRETION AND BLOOD LOSS

Physiological iron excretion is probably negligible during infancy, but blood loss of any sort imposes an increased need for iron. The possibility of blood loss should be considered in every infant or child with severe iron deficiency. Wilson and associates have described a syndrome of chronic blood loss due to gastrointestinal intolerance to whole cows milk and believe it to be a common cause of iron deficiency anemia. A lively controversy is now in progress concerning the importance of this condition. Diamond states that he has recognized it only once or twice in his large experience and believes blood loss is a secondary gastrointestinal manifestation of iron deficiency rather than a primary cause. The prevalence of this syndrome must be determined in anemic infants before its importance as a cause of iron deficiency anemia can be established. In some areas of the country hookworm infestation may be a common cause of iron deficiency.

IRON CONTENTS OF FOODS

Human and cows milk contain little iron (about 1.5 mg/l and 0.5 mg/l, respectively). About 15 quarts of cows milk would have to be consumed each day to provide enough iron to meet the requirements of normal infants during the first year of life! When milk accounts for a large proportion of the infant’s calories, the diet will performe be grossly deficient in iron. The most important source of iron in the diet of American infants is cereal that has been artificially fortified with reduced iron or iron-pyrophosphate during processing. Such cereals contain 8.6 to 22 mg of iron in each dry ounce. Limited amounts of eggs and meats are ordinarily consumed during the first year of life and so usually contribute a relatively small proportion of the total iron requirements. Although it is sometimes believed that the child receiving only human milk does not become iron deficient, there is little published data to support this opinion. In fact, in a small series of patients, Moe has shown the same incidence of iron deficiency in babies fed human milk as in those fed cows milk.

It has not been widely appreciated that methods of preparation and cooking affect the iron content of foods. Although Moore has reported that the iron content of some acid foods prepared at home in iron utensils may be increased 30 to 100 times over that of the same food cooked in glass or aluminum utensils, the effect of cooking vessels on iron content of ordinary foods is far less striking. In certain geographic regions, a high iron level in soil or water may increase the iron content of the diet sufficiently to invalidate calculations of dietary iron based only on food composition tables. In fact, “contamination” of foods by non-food iron may represent a most significant source of iron, although the strict sanitary methods which are used for modern food processing in fact result in exclusion of much iron from the diet. A recent study showing a striking geographic variability in the prevalence of anemia in preschool American children supports the thesis that local factors may appreciably affect iron balance.

IRON REQUIREMENTS

The amount of iron which should be provided by the infant’s diet has been estimated by two different methods with similar results. The first involves calculations based upon estimates of the infant’s average body iron content at birth and at 1 year of age. The difference between these two values approximates the net increase in body iron which must be realized from the diet during the first year of life. Using this approach, Schulman derived a value of 0.8 mg/day which must be absorbed by infants to supply the amount needed after the iron derived from the high concentration of hemoglobin at birth has been reclaimed for
hemoglobin synthesis. Thus, he calculated that the daily diet of the normal term infant must contain 8 mg of iron by 6 months of age. The term infant with a low initial iron endowment requires this amount by 3 to 4 months of age, and the low birth weight infant, requires this amount by 2 months of age. Gairdner, using similar calculations, arrived at a comparable requirement.46

The second method of determining dietary iron requirements has involved the administration of various amounts of iron to groups of infants and observation of effects on hemoglobin concentration. In extensive studies of this type Sturgeon4 demonstrated that highest hemoglobin levels were attained by infants who consistently received daily iron intake of about 1.0 mg/kg. Based upon an absorption efficiency of 10%, an intake of 1.0 mg/kg/day to a maximum of 15 mg, if begun at an appropriate time with respect to initial iron endowment, will provide sufficient iron to maintain normal hemoglobin values in most infants. This figure allows some leeway for individual variability in absorption and iron endowment. A somewhat greater allowance (2.0 mg/kg/day begun by age 2 months to a maximum of 15 mg) is advisable for low birth weight infants, for infants with low initial hemoglobin values, and for those who have experienced significant blood loss. In 1960, the Committee on Nutrition recommended an iron intake of 1.5 mg/kg/day for all infants.9 Because of the rather marked differences between the iron needs of normal term infants and those infants who fall in the foregoing special categories, it is now believed that the separate recommendations should be stated.

SPECIFIC DIETARY RECOMMENDATIONS

Food naturally rich in iron such as meats and eggs are expensive and tend to be restricted especially in the diets of the poorer segments of the population. Although this memorandum deals with iron, it is obvious that nutritional adequacy cannot be assured by simple iron supplementation, and all elements of dietary intake must be considered. Iron content of a diet consisting primarily of unfortified milk is always inadequate. Even when a good mixed diet is consumed, the intake of iron does not usually exceed 6.0 mg per 1,000 kcal unless foods artificially enriched with iron are utilized.44 To meet the recommendations of this memorandum, iron supplemented foods are necessary during infancy.

Iron requirements of normal infants can be met in a number of ways. Daily consumption of ¾ oz dry weight of iron enriched baby cereal (2 to 3 dry tablespoons or 30 to 45 cc of reconstituted cereal) beginning by 6 weeks of age and progressively increasing to ½ oz dry weight (5 to 6 dry tablespoons or 60 to 90 cc of reconstituted cereal) by 6 months of age assures an adequate iron intake for all infants except those with low initial endowment. Commercial infant cereals provide 8.6 to 22 mg of iron/dry ounce of cereal.

Consumption of iron-enriched milk formulas also assures adequate iron intake. Several studies have indicated that iron-deficiency anemia can be prevented by the use of cows milk formula to which iron has been added.28,47 Because of the rather marked differences between the iron needs of normal term infants and those infants who fall in the foregoing special categories, it is now believed that the separate recommendations should be stated.

Unfortunately, because of cost or practice by mothers, these excellent sources are not regularly utilized. The consumption of iron-fortified baby cereals decreases markedly during the second 6 months of life, so that by 12 months of age most infants no longer receive these cereals.49 In common usage, few infants continue to receive proprietary milk formulas after 6 months of age.50 Although experience indicates that many robust infants consuming a balanced, varied diet with abundant meats and eggs may not develop iron deficiency anemia, pediatricians should emphasize the importance of inclusion in the diet of iron-supplemented foods for at least 18 months in order to assure optimal iron intake for their patients.

This Committee suggests the most effective way to prevent iron deficiency on a large scale is to provide an iron-fortified dietary staple which can be begun by 6
weeks of age for infant consumption. Milk or carbohydrate staples (cereal, bread, grits, rice) have been shown to be suitable for fortification. The most appropriate food selected for iron enrichment may vary in different sections of the country and in different ethnic and social groups. At present such supplemented food staples are not in general use and efforts to identify and develop suitable vehicles for enrichment are mandatory if optimal iron nutrition is to be assured. Research into the most suitable chemical form of the iron supplement must be continued, since absorption of several iron additives may vary considerably.51 The low birth weight infant and infants with reduced iron endowment, as previously described, need relatively larger amounts of iron. It is doubtful that diet alone, even when iron supplemented cereals are used, can provide sufficient iron for these greater requirements. Iron fortified milk or medicinal iron should be prescribed in order to assure an iron intake of at least 2 mg/kg/day to a maximum of 15 mg/day for infants with reduced iron endowment.

IRON DEFICIENCY AFTER INFANCY

Recent surveys from widely separated areas in the United States suggest that severe nutritional anemia is not an important universal problem by 4 to 6 years of age, even in children from low socioeconomic backgrounds. For example, in Chicago only 5.5% of such children had hematocrits below 32%, and the mean hematocrit (36%) for these children did not differ significantly from normal.45 This is in the same locale where a 25 to 30% incidence of severe iron deficiency of infancy has been described.7 Therefore, it seems likely that, except for anemias secondary to blood loss, symptomatic problems of iron nutrition in childhood are largely restricted to the first 2 years of life.

IRON THERAPY

When iron deficiency anemia is diagnosed, specific therapy is usually recommended. Oral therapy with simple ferrous salts (sulfate, gluconate, fumarate) provides an inexpensive and predictably satisfactory response. There is no evidence that addition of any trace metal, additional hematinic substance or vitamin, increases appreciably the clinical response to simple ferrous salts.44 Indeed, absorption of other iron compounds or chelates may be sub-optimal occasionally, and therapeutic "failures" may result when such compounds are used.52,53

The therapeutic dosage of iron must be calculated in terms of elemental iron. A total of 6 mg/kg/day of elemental iron given in three divided doses between meals provides an adequate amount of iron for the stimulated bone marrow to utilize.44 Doses in excess of 6 mg/kg/day will not result in a more rapid hematologic response and may, in fact, increase the possibility of intolerance when administered, although intolerance to oral iron is extremely rare in pediatric practice. Decreased absorption of oral iron has not been convincingly documented as a cause of iron deficiency or therapeutic failure.

Only one effective parenteral iron preparation, iron-dextran (Imferon) is currently available for pediatric use. Oncogenic properties of this preparation in experimental animals have not been substantiated in humans.55 However, there is no proof that the hematologic response to parenteral iron is significantly faster or more complete than that to properly administered oral iron, and its use for prophylaxis is unwarranted. In most instances the indication for administration of parenteral iron for treatment of infants and children is a social one; that is, a parent who for social or intellectual reasons cannot be relied upon to properly administer oral iron.

Medicinal iron should be continued for a month or so after normal hemoglobin levels have been attained to assure replacement of the child's iron stores. Although there are potential harmful effects of iron overload in the tissues of the body in the normal individual, these complications result only after very prolonged administration of large
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doses of medicinal iron. On the other hand, in chronic anemias such as thalassemia major, which are associated with greatly increased iron absorption, medicinal iron may significantly increase the body burden of iron and contribute to an earlier death.

Acute poisoning due to accidental ingestion of medicinal iron is a serious problem. The importance of keeping containers of iron medications from the reach of young children cannot be overemphasized.

SUMMARY

1. The iron endowment of the newborn is proportional to the initial hemoglobin mass. This in turn depends upon the birth weight and initial hemoglobin level. The presence of low birth weight or decreased hemoglobin level in the first few days of life may identify infants with special iron requirements during the first 18 months of life.

2. It is recommended that the diet of normal term infants provide 1.0 mg/kg/day of iron by 3 months of age to a maximum intake of 15 mg/day. This requirement can be easily met by inclusion in the diet of appropriate amounts of foods which have been enriched with iron, such as infant cereals or milk formulas.

3. Infants with low birth weight and others with reduced iron endowment require as much as 2.0 mg of iron per kilogram per day beginning by 2 months of age. This amount of iron will not ordinarily be provided by the diet, even if iron-supplemented cereals are given. Attainment of these larger amounts requires the use of medicinal iron or iron-supplemented milk formula.

4. Attention should be directed to providing a variety of iron-enriched dietary staples to be used routinely for feeding American infants during the period of life from 3 to 18 months of age and to more precisely determining the best form of iron supplementation. At the present time iron fortified baby cereals and milk formulas are the iron supplemented foods most generally available. These are not utilized by the segments of the American population which have the greatest need for them.

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