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RETENTION OF IRON BY INFANTS

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■ **Abstract** Throughout the world, the most common nutritional deficiency disorder of infants is iron deficiency. Developing effective strategies for preventing iron deficiency requires detailed knowledge of iron retention under ordinary living conditions. For the adult population, such knowledge is at an advanced stage, but relatively little is known about infants. Many reports of iron retention by infants have been based on the assumption that, as in normal and iron-deficient adults, 80%–100% of newly absorbed iron is promptly incorporated into circulating erythrocytes, but this assumption is not supported by available data. This communication presents a review of iron retention by term and preterm infants, as determined by metabolic balance studies or ^{59}Fe whole-body counting studies, and it explores the relationship between iron retention and postnatal age, iron nutritional status, iron intake (or dose), and type of feeding.

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INTRODUCTION

In both highly industrialized and less-industrialized countries, iron deficiency is the most common nutritional deficiency disorder of infants and young children. Within this age group, infants are at greatest risk because of rapid expansion of hemoglobin mass and the consequent high requirement for absorbed iron. Iron deficiency in infants is less prevalent and less severe in the United States now than it was in the past (35), but it still ranks as the leading nutritional deficiency disorder.

Until the 1960s, most infants in the United States were fed either infant formulas low in iron or cow milk, and it is therefore not surprising that many were iron deficient. Anemia in infancy was commonly defined as hemoglobin concentration less than 10 g/dl, and data indicating that the cause of the anemia was iron deficiency included abnormalities in erythrocyte morphology (hypochromia, anisocytosis, and poikilocytosis) and decreased iron saturation of transferrin (12). Even with this definition, iron-deficiency anemia was reported to be present in 20% or more of low-income infants and toddlers.

Subsequently, when it became widely appreciated that a decrease in hemoglobin concentration and morphologic changes in the erythrocytes occur only after iron stores have been exhausted, and that nearly all individuals with adequate iron stores will maintain a hemoglobin concentration of 11 g/dl or more, the aim in public health nutrition shifted from prevention of iron-deficiency anemia to prevention of iron deficiency. Efforts to prevent iron deficiency have seemed more urgent since an association has been established between iron-deficiency anemia during the first few years of life and delayed cognitive development (7, 29, 36, 43, 44), and although we do not yet know whether iron-deficiency anemia is a cause of delayed cognitive development or merely a marker for it, the possibility that the relationship is causal makes it urgent that strategies be developed to prevent iron deficiency in infants. Developing such prevention strategies requires knowledge of the requirement for absorbed iron and knowledge of iron absorption under ordinary feeding circumstances. Much less is known about these areas in infants and children than in adults.

DEFINITION OF IRON ABSORPTION

The extent of retention of an iron isotope given with or without food has generally been determined in 3–7 days by metabolic balance studies, or in about 2 weeks by whole-body counting after administration of ^{59}Fe. These studies have been referred to as studies of iron absorption. However, because excretion of an isotopic iron tracer and therefore, presumably, of iron continues for weeks after

administration of an oral dose (19), the proportion remaining in the body 3 or 4 days after ingestion is greater than that remaining 14 days after ingestion. To avoid the imprecise definition commonly used, we proposed that iron absorption be defined as entry of iron from the intestinal lumen into the enterocyte, with subsequent transfer of the iron from the enterocyte to the circulation (19). According to this definition, unabsorbed iron includes iron that fails to enter the enterocyte, as well as iron that enters the enterocyte but is returned to the intestinal lumen with exfoliation of the enterocyte. We define iron absorption as the iron retained by the body 4 days after an iron dose, believing that 4 days best corresponds to the timing of events in the uptake of iron by the enterocytes and the subsequent transfer of iron to the circulation.

The life span of intestinal mucosal cells in the adult human duodenum and jejunum is 5–7 days (32), and the life span of mucosal cells in similar locations (the major sites for iron absorption) in an infant's intestines is presumably no longer than that in an adult. It is known that uptake of an iron isotope by intestinal cells occurs primarily in enterocytes that have migrated to the tip of the villus and are by then 3–5 days old (34, 38, 52). Therefore, it is likely that fecal excretion of the isotope during the first 4 days after isotope administration consists of (*a*) isotope that never entered enterocytes, (*b*) isotope that entered the enterocytes but was returned to the lumen when the enterocytes were sloughed, and (*c*) a small amount of absorbed isotope that was re-excreted into the lumen. We suspect that fecal excretion of isotope during days 5–7 after isotope administration consists mainly of isotope that was present in sloughed enterocytes and isotope that was absorbed into the circulation and then re-excreted. Fecal enrichment beyond 7 days presumably consists almost entirely of re-excreted isotope. According to our definition, iron absorption is a subcategory of iron retention (i.e. the quantity of ingested iron retained in the body 4 days after administration). We believe that retention of iron over any other time interval should be designated iron retention rather than iron absorption, and the time over which retention was determined should be specified.

Although the distinction between iron absorption and iron retention is conceptually important, the difference in iron retention at 3 days and 14 days is generally less than the differences resulting from other factors both within and between studies, the most important being age, iron nutritional status, iron intake, size of iron dose in which an isotope is delivered, and timing of isotope administration. Therefore, with few exceptions, in the remainder of this article we avoid use of the word absorption and refer only to iron retention.

METHODS FOR DETERMINING IRON RETENTION

Iron retention can be determined by metabolic balance studies without or with use of an iron isotope, by whole-body counting for ^{59}Fe, or by a double-isotope method.

Iron-Retention Studies Without the Use of an Iron Isotope

Intake and fecal excretion of iron are determined over a specified time interval. Such studies have been performed in term (11, 30, 40, 50, 51, 54, 56) and preterm infants (5, 57). In the studies reported in the 1950s and earlier, the methods for determining iron content of food and feces lacked the precision of later methods. For example, in the meticulously conducted balance studies by Wallgren (56) with exclusively breast-fed infants, the iron content of the milk was reported to be more than 0.5 mg/L in a number of samples obtained from women after the third month of lactation—values that seem most unlikely based on more recent studies of the iron content of human milk after the first few months of lactation (14). We have excluded the early studies from consideration.

Iron-Retention Studies with the Inclusion of an Iron Isotope

In iron-retention studies that include an iron isotope, it is possible to determine (*a*) iron retention from the whole diet (as is done in iron-balance studies without an iron isotope), (*b*) retention from an isotopically labeled dose of iron given between feedings, or (*c*) retention of iron from a feeding or feedings in which the isotope is included. Several groups of investigators have reported results of metabolic balance studies with an iron isotope in term (10, 20, 39, 49) and preterm (8, 21, 57) infants.

^{59}Fe Whole-Body Counting

With whole-body counting, ^{59}Fe, a gamma emitter, is administered orally and whole-body counting is subsequently performed to determine the quantity of ^{59}Fe remaining in the body. Such studies have been reported in term and preterm infants by Heinrich et al (25, 26) and Götze et al (22), and in term infants by Saarinen et al (47) and Saarinen & Siimes (46).

Double-Isotope Method

In the method of Saylor & Finch (48), one iron isotope is administered intravenously and another orally. Subsequently, erythrocyte incorporation of both isotopes is determined and the assumption is made that the same percentage of the intravenously administered isotope and of the retained amount of the orally administered isotope is incorporated into erythrocytes. Thus, the ratio of erythrocyte incorporation of the orally administered isotope to that of the intravenously administered isotope is the fraction of the orally administered isotope retained by the body, and it is therefore possible to determine retention of the orally administered isotope without fecal collection or whole-body counting. This approach has not been carried out with term infants, but there are two reports (41, 58) concerning preterm infants.

All the approaches to determining iron retention are subject to procedural and methodological errors. In balance studies that do not include administration of an isotope, the major difficulties are in obtaining accurate determinations of iron

intake and its fecal excretion. The errors in intake can be minimized by the inclusion of an iron isotope, but this inclusion does little to minimize the errors in fecal collection. Accurate results with ^{59}Fe whole-body counting require meticulous attention to calibration of the counter, inclusion of a preliminary count in the first 24 h after administration, and a final count at a designated time (nearly always 10–14 days) after ^{59}Fe administration. The double-isotope method of Saylor & Finch (48) has been validated in adults under precisely defined conditions (37, 42), but it has not been validated in infants or children. Moreover, procedures involving the provision of substantial amounts of an iron isotope intravenously over the course of 12–24 h (58) and the nonconcurrent administration of oral and intravenous doses of isotope (41) have not been validated even in adults. We have therefore excluded from consideration the two studies of preterm infants.

In addition to these three "direct" methods of determining iron retention, erythrocyte incorporation of an iron isotope is widely used as a surrogate for retention of the isotope. The approach is based on the assumption that 80%–100% of an absorbed isotope is present in circulating erythrocytes 10–14 days after isotope administration, an assumption that has been shown to be valid in normal and iron-deficient adults (23, 33, 37). As we discuss, the assumption that 80%–100% of retained iron is promptly incorporated into erythrocytes is not valid in term (19) or preterm (8, 21, 57) infants, and has not been tested in children beyond infancy. However, recent data (19) indicate that in infants (as in adults), when conditions of study are similar, erythrocyte incorporation of iron is correlated with retention. We therefore include studies of erythrocyte incorporation of iron and studies of iron retention in summarizing the effects of age, of iron intake, and of foods on iron retention.

REVIEW OF IRON-RETENTION STUDIES WITH INFANTS

Iron-retention studies with infants are summarized in Table 1. We have ignored reports that include four or fewer balance studies with infants. Because results of iron-retention studies are generally skewed toward higher values, geometric means are preferable to the somewhat greater arithmetic means; however, because most of the means reported in the literature are arithmetic, we present arithmetic means. Although some of the reports of iron-balance studies include urinary excretion, the quantities of iron excreted in urine are a trivial fraction of those excreted in feces, and we ignore urinary excretion.

Small Dose of an Iron Isotope Given Between Feedings

Studies in which a small dose of isotopically labeled iron is given between feedings reveal little about the practical consideration of iron retention from the whole diet; nevertheless, such studies are useful in exploring the effects of age, iron nutritional status, size of iron dose in which isotope is included, and type of feeding (e.g. human milk, infant formula) that precedes and follows isotope administration.

TABLE 1 Iron retention by term and preterm infants[a]

Determinant	No. of subjects	No. of studies	Age[c]	Weight[b] (g)	Duration of study (days)	Iron intake[b] (mg)	Retention (% intake)[b]	Comment
Small dose of iron isotope between feedings[c]								
Garby & Sjolin (20)[d]	12	12	10–90 days	NG	3	10.12 μg	53.7 (25.1)	Iron intake refers to ^{59}Fe-labeled test dose
Götze et al (22)[e]	33	33	<1 mo	NG	14	0.56	18 (7)	Birth weight >2500 g
	27	27	<1 mo	NG	14	0.56	17 (7)	Birth weight <2500 g
	42	42	1–3 mo	NG	14	0.56	30 (12)	Birth weight >2500 g
	32	32	1–3 mo	NG	14	0.56	40 (20)	Birth weight <2500 g
	25	25	3–6 mo	NG	14	0.56	37 (16)	Birth weight >2500 g
	11	11	3–6 mo	NG	14	0.56	64 (17)	Birth weight <2500 g
Saarinen et al (47)[f]	18	18	5.9–7.3 mo	7500 (1273)	14	Trace	38.1 (27.6)	Breast-fed infants
	16	16	5.9–7.3 mo	8000 (800)	14	Trace	19.5 (20.8)	Formula-fed infants
Iron retention from the diet: human milk								
Schulz-Lell et al (50)[g]	10	39	15–112 days	<4000–>6800	3	See comment	51.2 (33.9)	Iron intake about 0.07 mg kg^{-1} day^{-1}
Saarinen et al (47)[f]	11	11	5.9–7.3 mo	7900 (663)	14	Trace	48.8 (26.2)	Isotope given with feeding
Dauncey et al (5)[h]	6	12	10–30 days	NG	3	0.073 (0.0187)	See comment	Preterm infants iron intake in mg kg^{-1} day^{-1}; retention negative in 11 of 12 studies
	2	6	10–28 days	NG	5	0.10	54.0 (17.2)	Small-for-gestational-age age infants; iron intake in mg kg^{-1} day^{-1}

	5	18	30–72 days	NG	3	8.08 (2.91)	22.2 (15.1)	Preterm infants given supplemental iron; iron intake in mg kg^{-1} day^{-1}
Iron retention from the diet: formula								
Schulz-Lell et al (50)[g]	4	15	15–115 days	<3300–>6800	3	See comment	34.0 (20.8)	Fed formula supplemented with iron; iron intake about 1.82 mg kg^{-1} day^{-1}
Schulz-Lell et al (51)[g]	7	30	15–115 days	NG	3	See comment	36	Formula containing bovine lactoferrin; iron intake about 0.17 mg kg^{-1} day^{-1}
	9	28	15–115 days	NG	3	See comment	28	Formula unsupplemented with bovine lactoferrion; iron intake about 0.12 mg kg^{-1} day^{-1}
Saarinen & Siimes (46)[f]	10	10	11–13 mo	9000–11,000	14	See comment	12.5 (9.2)	0.04 mg of iron in 50-ml test feeding
	9	9	11–13 mo	9000–11,500	14	See comment	9.2 (10.5)	0.34 mg of iron in 50-ml test feeding
	10	10	11–13 mo	8100–11,500	14	See comment	6.7 (4.4)	0.64 mg of iron in 50-ml test feeding
Fairweather-Tait et al (10)[h]	16	16	7 days	2060–3500	3	165 μg/day	44.4 (25.8)	Formula with ^{58}Fe-labeled ferric chloride
	13	13	7 days	2660–4000	3	192 μg/day	46.2 (23.9)	Formula with ^{58}Fe-labeled bovine lactoferrin

(*Continued*)

TABLE 1 (*Continued*)

Determinant	No. of subjects	No. of studies	Age[c]	Weight[b] (g)	Duration of study (days)	Iron intake[b] (mg)	Retention (% intake)[b]	Comment
Iron retention from the diet: Beikost								
Martinez et al (39)[j]	8	8	6 mo	8250 (410)	7	2.9–3.4 mg/meal	17.0 (11.1)	Meat-containing meals with added heme iron
	8	8	6 mo	7780 (920)	7	2.9–3.4 mg/meal	28.4 (12.7)	Meat-containing meals with added ferrous sulfate

[a]See Table 2 for the following: Fomon et al (19), term infants; Gorten et al (21), preterm infants; Ehrenkranz et al (8), preterm infants; and Widness et al (57), preterm infants.

[b]Values in parentheses are standard deviations.

[c]When no isotope was given, age at start of fecal collection; otherwise age at time of isotope administration. NG, Not given.

[d]Breast-fed and formula-fed term infants; balance studies with ^{59}Fe.

[e]^{59}Fe-labeled iron (0.56 mg) given with 18 mg of ascorbic acid after a 6-h fast; retention determined by whole-body counting.

[f]Term infants; ^{59}Fe whole-body counting.

[g]Term infants; balance studies, no iron isotope.

[h]Preterm and small-for-gestational-age infants; balance studies, no iron isotope.

[i]Term infants; ^{58}Fe balance studies.

[j]Balance studies; meals labeled with ^{57}Fe.

In the great majority of the studies, ascorbic acid was included with the dose to enhance iron absorption.

Garby & Sjolin (20) reported a mean retention of 53.7% of intake in 10- to 90-day-old infants (Table 1), and Fomon et al (19) reported a mean retention (at 11 days) of 27.8% in 20- to 69-day-old infants and 32.5% in 165- to 215-day-old infants (Table 2). Gorten et al (21) reported a mean retention of 23.1% of intake by preterm infants with reticulocyte counts less than 5% and 37.8% of intake for infants with reticulocyte counts greater than 5% (Table 2). In more recent studies of preterm infants, Ehrenkranz et al (8) reported a mean retention of 41.6% of a dose of ^{58}Fe given between feedings, and Widness et al (57) reported a mean retention of 34.0% of a dose given 1 h after interruption of continuous nasogastric feedings (Table 2.)

TABLE 2 Retention, erythrocyte incorporation, and utilization of an administered iron isotope by term and preterm infants

Determinants	Fomon et al (19) (term)		Gorten et al (21) (preterm)		Ehrenkranz et al (8) (preterm)	Widness et al (57) (preterm)
No. subjects[a]	9	9	6[b]	8[c]	11	10
Age (days)[d]						
Mean	41	191	18	38	26	23
SD	14	20	10	15	14	6
Weight (g)[e]						
Mean	4823	8471	1545	1341	1431	975
SD	814	618	361	289	150	105
Duration of study (days)	11	11	8–14	7–9	7	10
Retention (%)[f]						
Mean	27.8	32.5	23.1	37.8	41.6	34.0
SD	7.6	16.2	14.5	20.6	17.6	7.9
Erythrocyte incorporation (%)[f]						
Mean	7.1	26.5	6.5	21.9	12.0	4.0
SD	6.0	9.8	3.8	12.6	9.6	1.8
Utililization (%)[g]						
Mean	23.1	51.9	40.0	55.4	28.7	12.1
SD	13.9	28.4	33.6	21.7	22.3	7.2

[a]One study with each infant except for Widness et al, in which three subjects were studied twice; one study with 121% utilization has been omitted from the summary.

[b]Reticulocyte count less than 5%.

[c]Reticulocyte count more than 5%.

[d]Postnatal age at time of isotope administration. SD, standard deviation of the mean.

[e]Weight at time of isotope administration, except value for Gorten et al is birth weight.

[f]Percentage of intake.

[g]Erythrocyte incorporation divided by retention $\times 100$.

TABLE 3 Retention of an iron isotope by term infants in relation to iron nutritional status, size of iron dose, and effect of formula[a]

		Retention of ^{59}Fe (% dose)							
		Iron sufficient				Iron deficient			
		Without formula		With formula		Without formula		With formula	
Age (month)	Dose (mg)	No.[b]	Mean[c]	No.	Mean	No.	Mean	No.	Mean
3–6[d]	0.56	15	25.6 (9.3)			11	49.5 (13.7)		
1–18[e]	5.0	3	18.0 (5)	3	3.8 (2.0)	9	26 (8.4)	9	8.5 (4.1)
1–18[e]	10	12	7.6 (1.7)			4	19 (8.6)		

[a]^{59}Fe dose given after a fast with or without 50 ml of milk-based formula; retention determined by whole-body counting 2 weeks after isotope administration.

[b]Number of subjects; one study per subject.

[c]Values in parentheses are standard deviations.

[d]Data of Götze et al (22) (see Table 1).

[e]Data of Heinrich et al (26).

The whole-body counting studies of Heinrich and coworkers (22, 24–26) are of particular interest because they were carried out with great care, and whole-body counting was done before ^{59}Fe administration (permitting correction for background) as well as 8–12 h and 14 days after ^{59}Fe administration (24). Heinrich et al (25) determined iron retention with a large number of term and preterm infants after administration of 0.56 mg of ^{59}Fe-labeled ferrous iron given after a 6-h fast. The data plus some additional data were summarized by Götze et al (22) and are presented in Table 1. Iron retention by infants with birth weights more than 2500 g averaged 18% of intake by those less than 1 month of age, 30% of intake by those from 1 to 3 months of age, and 37% by those from 3 to 6 months of age. Corresponding values for infants with birth weights less than 2500 g were 17%, 40%, and 64%. Heinrich et al (26) also administered larger doses of iron after a fast and reported mean retention in 1- to 18-month-old iron-sufficient infants of 18% of intake with a 5-mg dose and 7.6% of intake with a 10-mg dose (Table 3). In iron-deficient infants of similar age, retention was 26% of intake with a 5-mg dose and 19% of intake with a 10-mg dose. Saarinen et al (47) reported retention of 38.1% by 6- to 7-month-old breast-fed infants and of 19.5% by formula-fed infants given a very small dose of ^{59}Fe between feedings.

Iron Retention from the Diet—Human Milk

Schulz-Lell et al (50) reported mean iron retention of 51.2% of intake by term breast-fed infants 15–112 days old, and Saarinen et al (47) reported retention of

48.8% by 6- to 7-month-old infants given a very small dose of ^{59}Fe with a breast feeding (Table 1). Iron retention was found by Dauncey et al (5) to be less than intake in 11 of 12 balance studies with 10- to 30-day-old preterm infants fed human milk. In small-for-gestational-age infants aged 10–28 days, mean retention was 54% of intake, and in 30- to 72-day-old preterm infants fed human milk with supplemental iron, mean retention was 22.2% of intake.

Iron Retention from the Diet—Formula

In studies of infants at about 1 year of age, Saarinen & Siimes (46) reported that iron retention was 12% of intake from a formula with iron content of 0.8 mg/liter, 9% from a formula with iron content of 6.8 mg/liter, and 7% from a formula with iron content of 12.8 mg/liter (Table 1). Iron retention was thus inversely related to the iron content of the formula.

Fairweather-Tait et al (10) determined iron retention by 7-day-old term infants fed a formula with added bovine lactoferrin or a similar formula without bovine lactoferrin. The formulas were labeled with ^{58}Fe-ferric chloride or ^{58}Fe-bovine lactoferrin. There was no difference related to the presence of lactoferrin. Mean retention of ^{58}Fe was 44.4% with ^{58}Fe-labeled ferric chloride and 46.2% with ^{58}Fe-labeled bovine lactoferrin. The means were substantially increased by several high retention values, which the authors suggested were the result of incomplete fecal collections (10). We consider it unlikely that the extent of incomplete collections was sufficient to invalidate the conclusion that even 7-day-old infants retain substantial amounts of orally administered iron. Schulz-Lell et al (50) reported mean iron retention of 34% by four term infants fed formula with iron content of 10.3 mg/liter.

The effect of infant formula on retention of an iron isotope is evident from the data of Heinrich et al (26) (Table 3). When a 5-mg dose of ^{59}Fe-labeled ferrous iron was given alone to 1- to 18-month-old iron-sufficient subjects after a fast, mean retention as determined by whole-body counting was 18% of intake. When the same dose was given with a 50-ml feeding of a milk-based formula, mean retention was 3.8%. In iron-deficient subjects, retention of a 5-mg dose of iron was 26% of intake when given without food and 19% of intake when given with 50 ml of milk-based formula.

Iron Retention from the Diet—Beikost

Martinez et al (39) carried out 7-day iron-balance studies with breast-fed or formula-fed 6-month-old term infants. The subjects were fed meat-containing meals fortified with a heme iron concentrate or with ferrous sulfate. Mean iron retention was 17% of intake by infants fed the heme iron-containing meals and 28.4% of intake by infants fed the ferrous sulfate-containing meals.

RELATION OF IRON RETENTION TO TYPE OF FEEDING, AGE, IRON NUTRITIONAL STATUS, PREMATURITY, AND IRON DOSE

Effect of Food, Type of Feeding

Because of the presence of inhibitors of nonheme iron absorption in infant foods, there is less retention of an iron isotope when it is given with a feeding than when it is given between feedings. A possible exception is human milk, which has a low content of inhibitors of nonheme iron retention. The data summarized in Table 1 show that retention of iron from human milk is comparable to the retention of small doses of isotope given between feedings.

Retention of an iron isotope given with formula, on the other hand, is markedly less than retention of an isotope given between feedings. The data of Heinrich et al (26) demonstrate the major inhibition of retention resulting from giving only 50 ml of a milk-based formula (Table 3).

Even when an iron isotope is given to infants between feedings, the milk, formula, or other food consumed before and after the dose will influence iron retention, presumably because the iron from the administered dose comes into contact in the intestinal tract with dietary inhibitors of iron absorption. Saarinen et al (47) reported that when a small dose of isotope was given between feedings, mean retention was 38.5% of intake by breast-fed infants and 19.5% of intake by formula-fed infants (Table 1). Although we did not determine retention in our study of 56-day-old breast-fed and formula-fed infants who were given a dose of ^{58}Fe between feedings (15), erythrocyte incorporation of ^{58}Fe was significantly greater by breast-fed infants (20% of intake) than by formula-fed infants (6.9% of intake).

Age

The data of Götze et al (22) indicate that at least during the early months of life, retention of iron increases with age (Table 1). Retention of isotope by infants with birth weights more than 2500 g was 18% of intake during the first month of life, 30% of intake from 1 to 3 months, and 37% from 3 to 6 months of age (Table 1). Corresponding retentions by infants with birth weights less than 2500 g were 17%, 40%, and 64%. Although the age-related differences were not significant, the studies of Schulz-Lell et al (50) and Fomon et al (19) are consistent with the conclusion that retention is greater by older infants than by those in the first month or two of life.

Iron Nutritional Status

Because iron nutritional status of infants decreases with increasing age, the effect of age is nearly impossible to separate from the effect of iron nutritional status.

The data of Heinrich et al (26) indicate that in infants, as in adults, iron retention is correlated with iron nutritional status (Table 3). Iron-deficient subjects retained a greater percentage of iron than did iron-sufficient subjects in the following categories: 5-mg dose after a fast, 5-mg dose with formula, 10-mg dose after a fast.

Plasma ferritin concentration, at least after the first 2 months of life, appears in infants to reflect iron stores. Therefore, the finding by Fomon et al (19) that in infants from 165 to 215 days of age, iron retention 11 days after isotope administration was inversely related to plasma ferritin concentration is further evidence that in infants, as in adults, iron retention is inversely correlated with iron-nutritional status. In most of our studies of erythrocyte incorporation of ^{58}Fe by normal term infants (13, 15–17), incorporation was inversely correlated with plasma ferritin concentration, although in one study (18) the correlation was not significant.

Term Versus Preterm Infants

Although studies have not been designed to compare retention of iron by term and preterm infants, the data of Götze et al (22) suggest that after the first month of life, retention of iron may be somewhat greater by preterm than by term infants at the same postnatal age. Comparing the data of Fomon et al (19) concerning term infants with mean age of 41 days with those of Gorten et al (21), Ehrenkranz et al (8), and Widness et al (57) also suggests that at similar postnatal ages, retention is somewhat greater by preterm than by term infants (Table 2).

Iron Dose/Iron Concentration of Feeding

It has long been recognized that in adults, the percentage of retention of an orally administered dose of iron is inversely correlated with the size of the dose (3, 4, 53). Several studies suggest that in infants, as in adults, the percentage of retention of iron is inversely correlated with the size of the dose. As indicated in Table 3, the data of Götze et al (22) and Heinrich et al (26) show that mean retention of an isotope given between feedings was inversely related to the size of the dose, in both iron-sufficient and iron-deficient subjects whether the dose was given with or without formula. Furthermore, with a dose of 0.9 mg of ^{58}Fe-enriched ferrous sulfate, mean erythrocyte incorporation of ^{58}Fe was 16.5% of the dose (19), whereas in an earlier study under similar study conditions, a dose of 1.95 mg of ^{58}Fe-enriched ferrous sulfate (13) resulted in erythrocyte incorporation of 9.4% of the dose.

As noted above, Saarinen & Siimes (46) reported retentions of 12%, 9%, and 7% of intake, respectively, by infants fed formulas with iron concentrations of 0.8, 6.8, and 12.8 mg/liter (Table 1). Test meals of 50 ml of formula provided iron doses of 0.04, 0.34, and 0.64 mg, respectively.

ERYTHROCYTE INCORPORATION OF RETAINED IRON (UTILIZATION)

As previously mentioned, it is generally assumed (1, 2, 6, 9, 27, 28, 31, 45, 55) that 80%–100% of iron retained from an oral dose is promptly incorporated into erythrocytes (utilized). That this assumption is not valid for normal infants is evident from the studies summarized in Table 2. In 20- to 65-day-old term infants, isotope retention at 11 days was 27.8% of intake, and utilization was 23.1%, and in 165- to 215-day-old infants, retention was 32.5% of intake and utilization was 51.9% of intake (19). Similarly, in preterm infants, the prompt erythrocyte incorporation of retained iron is far less than the 80%–100% that has been commonly assumed.

In our study of infants fed iron-supplemented infant formulas (18), mean erythrocyte incorporation of ^{58}Fe from a formula with iron content of 12 mg/liter was 2.68% of intake, which amounted to 0.32 mg of iron per day. On the assumption that utilization was 80%, daily retention of iron would have been 0.4 mg/day. This mean retention is less than the estimated daily iron requirement (14) of 0.55–0.75 mg/day. As summarized previously (14), a number of studies have demonstrated that nearly all term infants fed formulas with an iron content of 12 mg/liter remain in good iron nutritional status, which would not be likely to be the case if the iron requirement has been correctly estimated and the mean retention from such formulas is only 0.4 mg/day. However, with the evidence that utilization is no greater than 50%, erythrocyte incorporation of 0.32 mg/day translates into retention of at least 0.64 mg/day.

SUMMARY

For more than 50 years, vigorous exploration of iron kinetics in adult subjects has been pursued with the aid of radioisotopes of iron. These studies have provided an understanding of iron metabolism and iron requirements of adults. They have also provided a sound basis for recommendations regarding the means of meeting the iron requirements of adults. Similar knowledge of infants and children has lagged far behind, at least in part because of the reluctance of most investigators to administer radioisotopes to normal infants or children. In fact, as is evident from the data presented in Tables 1 and 2, a high proportion of the most useful information available before the 1990s about iron retention by infants was the result of studies with the radioisotope, ^{59}Fe. Although methodology for determination of stable isotopes of iron came into widespread use in the 1980s, the first report of use of these stable isotopes in infants did not appear until 1987 (10). Despite the number of studies with stable isotopes of iron that were reported in the 1990s, our knowledge of factors affecting iron retention by infants remains rudimentary.

As indicated by this review, current knowledge regarding the absorption and short-term retention of iron permits the delineation of iron absorption under a number of circumstances. However, if we are to be more successful in preventing

iron deficiency in infants and preschool children, we will need to focus our efforts on obtaining a better understanding of postabsorptive metabolism of iron. For example, it has only recently been appreciated that infants promptly utilize a substantially lower proportion of absorbed iron than do adults. This finding mandates a change in thinking in the sense that, in infants and toddlers, absorbed iron is not an approximation of retained iron.

Before we can devise more successful strategies for the prevention of iron deficiency, an array of questions must be answered. What are the inevitable losses of iron from skin and gastrointestinal tract by infants? Such losses account for a substantial proportion of the requirement for absorbed iron during the first year of life. How does the timing of iron intake relate to iron retention under usual conditions of infant feeding? Can we achieve greater retention of iron by older infants if we devise feeding sequences that supply most of the dietary iron at times other than those that provide the major inhibitors of nonheme iron absorption? Can we define circumstances in infancy, as they have been defined in adults, in which an estimate of iron retention can be made from erythrocyte incorporation of iron?

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