13. Iron

13.1 Role of iron in human metabolic processes

Iron has several vital functions in the body. It serves as a carrier of oxygen to the tissues from the lungs by red blood cell haemoglobin, as a transport medium for electrons within cells, and as an integrated part of important enzyme systems in various tissues. The physiology of iron has been extensively reviewed (*1–6*).

Most of the iron in the body is present in the erythrocytes as haemoglobin, a molecule composed of four units, each containing one haem group and one protein chain. The structure of haemoglobin allows it to be fully loaded with oxygen in the lungs and partially unloaded in the tissues (e.g. in the muscles). The iron-containing oxygen storage protein in the muscles, myoglobin, is similar in structure to haemoglobin but has only one haem unit and one globin chain. Several iron-containing enzymes, the cytochromes, also have one haem group and one globin protein chain. These enzymes act as electron carriers within the cell and their structures do not permit reversible loading and unloading of oxygen. Their role in the oxidative metabolism is to transfer energy within the cell and specifically in the mitochondria. Other key functions for the iron-containing enzymes (e.g. cytochrome P450) include the synthesis of steroid hormones and bile acids; detoxification of foreign substances in the liver; and signal controlling in some neurotransmitters, such as the dopamine and serotonin systems in the brain. Iron is reversibly stored within the liver as ferritin and haemosiderin whereas it is transported between different compartments in the body by the protein transferrin.

13.2 Iron metabolism and absorption

13.2.1 Basal iron losses

Iron is not actively excreted from the body in urine or in the intestines. Iron is only lost with cells from the skin and the interior surfaces of the body—intestines, urinary tract, and airways. The total amount lost is estimated at 14 µg/kg body weight/day (*7*). In children, it is probably more correct to relate these losses to body surface. A non-menstruating 55-kg woman loses about

0.8 mg Fe/day and a 70-kg man loses about 1 mg/day. The range of individual variation has been estimated to be ±15% (*8*).

Earlier studies suggested that sweat iron losses could be considerable, especially in a hot, humid climate. However, new studies which took extensive precautions to avoid the interference of contamination of iron from the skin during the collection of total body sweat have shown that sweat iron losses are negligible (*9*).

13.2.2 Requirements for growth

The newborn term infant has an iron content of about 250–300 mg (75 mg/kg body weight). During the first 2 months of life, haemoglobin concentration falls because of the improved oxygen situation in the newborn infant compared with the intrauterine fetus. This leads to a considerable redistribution of iron from catabolized erythrocytes to iron stores. This iron will cover the needs of the term infant during the first 4–6 months of life and is why iron requirements during this period can be provided by human milk, which contains very little iron. Because of the marked supply of iron to the fetus during the last trimester of pregnancy, the iron situation is much less favourable in the premature and low-birth-weight infant than in the healthy term infant. An extra supply of iron is therefore needed in these infants during the first 6 months of life.

In the term infant, iron requirements rise markedly after age 4–6 months and amount to about 0.7–0.9 mg/day during the remaining part of the first year. These requirements are very high, especially in relation to body size and energy intake (Table 13.1) (*10*).

In the first year of life, the term infant almost doubles its total iron stores and triples its body weight. The increase in body iron during this period occurs mainly during the latter 6 months. Between 1 and 6 years of age, the body iron content is again doubled. The requirements for absorbed iron in infants and children are very high in relation to their energy requirements. For example, in infants 6–12 months of age, about 1.5 mg of iron need to be absorbed per 4.184 MJ and about half of this amount is required up to age 4 years.

In the weaning period, the iron requirements in relation to energy intake are at the highest level of the lifespan except for the last trimester of pregnancy, when iron requirements to a large extent have to be covered from the iron stores of the mother (see section 13.4 on iron and pregnancy). Infants have no iron stores and have to rely on dietary iron alone. It is possible to meet these high requirements if the diet has a consistently high content of meat and foods rich in ascorbic acid. In most developed countries today, infant

TABLE 13.1

Iron intakes required for growth under the age of 18 years, median basal iron losses, menstrual losses in women, and total absolute iron requirements

Group	Age (years)	Mean body weight (kg)	Required iron intakes for growth (mg/day)	Median basal iron losses (mg/day)	Menstrual losses		Total absolute requirements[a]	
					Median (mg/day)	95th percentile (mg/day)	Median (mg/day)	95th percentile (mg/day)
Infants and children	0.5–1	9	0.55	0.17			0.72	0.93
	1–3	13	0.27	0.19			0.46	0.58
	4–6	19	0.23	0.27			0.50	0.63
	7–10	28	0.32	0.39			0.71	0.89
Males	11–14	45	0.55	0.62			1.17	1.46
	15–17	64	0.60	0.90			1.50	1.88
	18+	75		1.05			1.05	1.37
Females	11–14[b]	46	0.55	0.65			1.20	1.40
	11–14	46	0.55	0.65	0.48[c]	1.90[c]	1.68	3.27
	15–17	56	0.35	0.79	0.48[c]	1.90[c]	1.62	3.10
	18+	62		0.87	0.48[c]	1.90[c]	1.46	2.94
Postmenopausal		62		0.87			0.87	1.13
Lactating		62		1.15			1.15	1.50

[a] Total absolute requirements = Requirement for growth + basal losses + menstrual losses.
[b] Pre-menarche.
[c] Effect of the normal variation in haemoglobin concentration not included in this figure.
Source: adapted, in part, from reference (*8*) and in part on new calculations of the distribution of iron requirements in menstruating women.

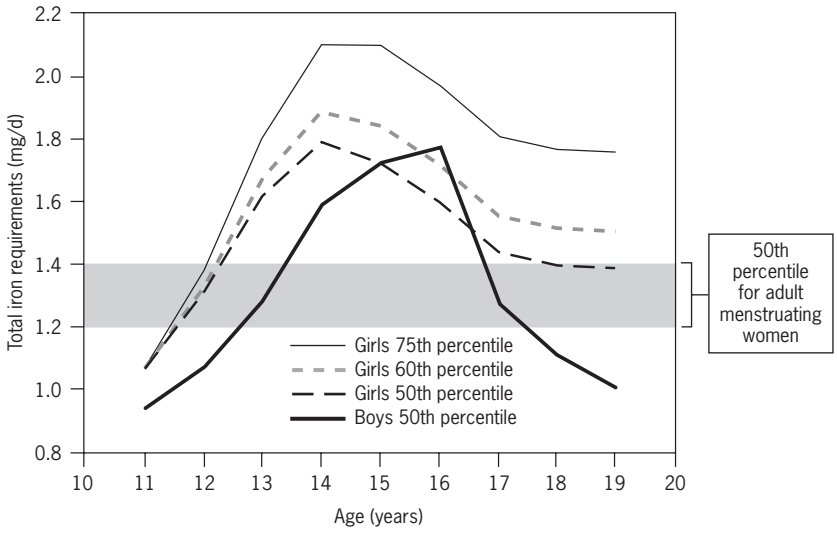
cereal products are the staple foods for that period of life. Commercial products are regularly fortified with iron and ascorbic acid, and they are usually given together with fruit juices and solid foods containing meat, fish, and vegetables. The fortification of cereal products with iron and ascorbic acid is important in meeting the high dietary needs, especially considering the importance of an optimal iron nutrititure during this phase of brain development.

Iron requirements are also very high in adolescents, particularly during the period of rapid growth (*11*). There is a marked individual variation in growth rate, and the requirements of adolescents may be considerably higher than the calculated mean values given in Table 13.1. Girls usually have their growth spurt before menarche, but growth is not finished at that time. Their total iron requirements are therefore considerable. In boys during puberty there is a marked increase in haemoglobin mass and concentration, further increasing iron requirements to a level above the average iron requirements in menstruating women (Figure 13.1).

13.2.3 Menstrual iron losses

Menstrual blood losses are very constant from month to month for an individual woman but vary markedly from one woman to another (*16*). The main part of this variation is genetically controlled by the fibrinolytic activators in

FIGURE 13.1
Iron requirements of boys and girls at different ages



Sources: based on data from references (*8* and *12–16*).

the uterine mucosa—even in populations which are geographically widely separated (Burma, Canada, China, Egypt, England, and Sweden) (*17*, *18*). These findings strongly suggest that the main source of variation in iron status in different populations is not related to a variation in iron requirements but to a variation in the absorption of iron from the diets. (This statement disregards infestations with hookworms and other parasites.) The mean menstrual iron loss, averaged over the entire menstrual cycle of 28 days, is about 0.56 mg/day. The frequency distribution of physiological menstrual blood losses is highly skewed. Adding the average basal iron loss (0.8 mg/day) and its variation allows the distribution of the total iron requirements in adult women to be calculated as the convolution of the distributions of menstrual and basal iron losses (Figure 13.2). The mean daily total iron requirement is 1.36 mg. In 10% of women, it exceeds 2.27 mg and in 5% it exceeds 2.84 mg (*19*). In 10% of menstruating (still-growing) teenagers, the corresponding daily total iron requirement exceeds 2.65 mg, and in 5% of girls, it exceeds 3.2 mg. The marked skewness of menstrual losses is a great nutritional problem because assessment of an individual's iron losses is unreliable. This means that women with physiological but heavy losses cannot be identified and reached by iron supplementation. The choice of contraceptive method also greatly influences menstrual losses.

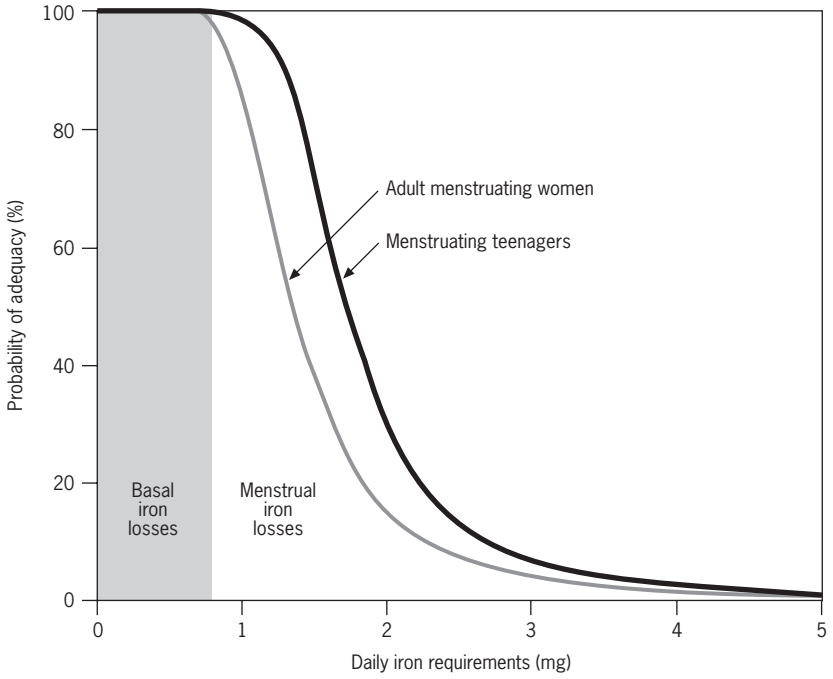
In postmenopausal women and in physically active elderly people, the iron requirements per unit of body weight are the same as in men. When physical activity decreases as a result of ageing, blood volume decreases and haemoglobin mass diminishes, leading to a shift of iron usage from haemoglobin and muscle to iron stores. This implies a reduction of the daily iron requirements. Iron deficiency in the elderly is therefore seldom of nutritional origin but is usually caused by pathologic iron losses.

The absorbed iron requirements in different groups are summarized in Table 13.1. The iron requirements during pregnancy and lactation are dealt with separately (see section 13.4).

13.2.4 Iron absorption

With respect to the mechanism of absorption, there are two kinds of dietary iron: haem iron and non-haem iron (*20*). In the human diet, the primary sources of haem iron are the haemoglobin and myoglobin from consumption of meat, poultry, and fish whereas non-haem iron is obtained from cereals, pulses, legumes, fruits, and vegetables. The average absorption of haem iron from meat-containing meals is about 25% (*21*). The absorption of haem iron can vary from about 40% during iron deficiency to about 10% during iron repletion (*22*). Haem iron can be degraded and converted to non-haem

FIGURE 13.2
Distribution of daily iron requirements in menstruating adult women and teenagers: the probability of adequacy at different amounts of iron absorbed



The left-hand side of the graph shows the basal obligatory losses that amount to 0.8 mg/day. The right-hand side shows the variation in menstrual iron losses. This graph illustrates that growth requirements in teenagers vary considerably at different ages and between individuals.

iron if foods are cooked at a high temperature for too long. Calcium (discussed below) is the only dietary factor that negatively influences the absorption of haem iron and does so to the same extent that it influences non-haem iron (*23*).

Non-haem iron is the main form of dietary iron. The absorption of non-haem iron is influenced by individual iron status and by several factors in the diet. Dietary factors influencing iron absorption are outlined in Box 13.1. Iron compounds used for the fortification of foods will only be partially available for absorption. Once dissolved, however, the absorption of iron from fortificants (and food contaminants) is influenced by the same factors as the iron native to the food substance (*24*, *25*). Iron from the soil (e.g. from various forms of clay) is sometimes present on the surface of foods as a contaminant, having originated from dust on air-dried foods or from the residue of the water used in irrigation. Even if the fraction of iron that is available is often

BOX 13.1 FACTORS INFLUENCING DIETARY IRON ABSORPTION

Haem iron absorption

Factors determining iron status of subject:

Amount of dietary haem iron, especially from meat

Content of calcium in meal (e.g. from milk, cheese)

Food preparation (i.e. time, temperature)

Non-haem iron absorption

Factors determining iron status of subject:

Amount of potentially available non-haem iron (includes adjustment for fortification iron and contamination iron)

Balance between the following enhancing and inhibiting factors:

Enhancing factors

Ascorbic acid (e.g. certain fruit juices, fruits, potatoes, and certain vegetables)

Meat, fish and other seafood

Fermented vegetables (e.g. sauerkraut), fermented soy sauces, etc.

Inhibiting factors

Phytate and other lower inositol phosphates (e.g. bran products, bread made from high-extraction flour, breakfast cereals, oats, rice – especially unpolished rice – pasta products, cocoa, nuts, soya beans, and peas)

Iron-binding phenolic compounds (e.g. tea, coffee, cocoa, certain spices, certain vegetables, and most red wines)

Calcium (e.g. from milk, cheese)

Soya

Source: reference (*23*).

small, contamination iron may still be nutritionally significant because of its addition to the overall dietary intake of iron (*26*, *27*).

Reducing substances (i.e. substances that keep iron in the ferrous form) must be present for iron to be absorbed (*28*). The presence of meat, poultry, and fish in the diet enhance iron absorption. Other foods contain chemical entities (ligands) that strongly bind ferrous ions, and thus inhibit absorption. Examples are phytates and certain iron-binding polyphenols (see Box 13.1).

13.2.5 Inhibition of iron absorption

Phytates are found in all kinds of grains, seeds, nuts, vegetables, roots (e.g. potatoes), and fruits. Chemically, phytates are inositol hexaphosphate salts

and are a storage form of phosphates and minerals. Other phosphates have not been shown to inhibit non-haem iron absorption. In North American and European diets, about 90% of phytates originate from cereals. Phytates strongly inhibit iron absorption in a dose-dependent fashion and even small amounts of phytates have a marked effect (*29*, *30*).

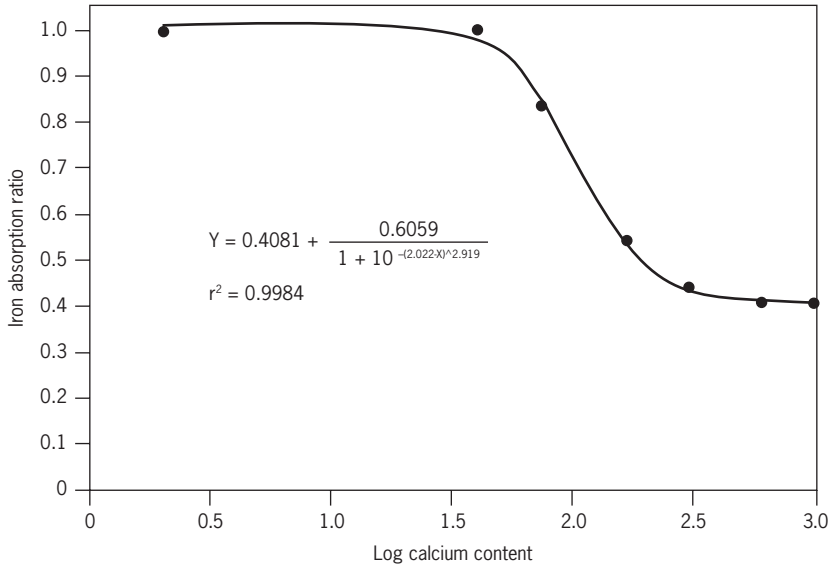
Bran has a high content of phytate and strongly inhibits iron absorption. Wholewheat flour, therefore, has a much higher phytate content than does white-wheat flour (*31*). In bread, some of the phytates in bran are degraded during the fermentation of the dough. Fermentation for a couple of days (sourdough fermentation) can almost completely degrade the phytate and increase the bioavailability of iron in bread made from wholewheat flour (*32*). Oats strongly inhibit iron absorption because of their high phytate content that results from native phytase in oats being destroyed by the normal heat process used to avoid rancidity (*33*). Sufficient amounts of ascorbic acid can counteract this inhibition (*34*). In contrast, non-phytate-containing dietary fibre components have almost no influence on iron absorption.

Almost all plants contain phenolic compounds as part of their defence system against insects and animals. Only some of the phenolic compounds (mainly those containing galloyl groups) seem to be responsible for the inhibition of iron absorption (*35*). Tea, coffee, and cocoa are common plant products that contain iron-binding polyphenols (*36–39*). Many vegetables, especially green leafy vegetables (e.g. spinach), and herbs and spices (e.g. oregano) contain appreciable amounts of galloyl groups, which strongly inhibit iron absorption as well. Consumption of betel leaves, common in areas of Asia, also has a marked negative effect on iron absorption.

Calcium, consumed as a salt or in dairy products interferes significantly with the absorption of both haem and non-haem iron (*40–42*). However, because calcium is an essential nutrient, it cannot be considered to be an inhibitor of iron absorption in the same way as phytates or phenolic compounds. In order to lessen this interference, practical solutions include increasing iron intake, increasing its bioavailability, or avoiding the intake of foods rich in calcium and foods rich in iron at the same meal (*43*).

The mechanism of action for absorption inhibition is unknown, but the balance of evidence strongly suggests that the inhibitory effect takes place within the mucosal cell itself at the common final transfer step for haem and non-haem iron. Recent analyses of the dose–effect relationship show that the first 40 mg of calcium in a meal does not inhibit absorption of haem and non-haem iron. Above this level of calcium intake, a sigmoid relationship develops, and at levels of 300–600 mg calcium, reaches a 60% maximal inhibition of iron absorption. The form of this curve suggests a one-site competitive

FIGURE 13.3
Effect of different amounts of calcium on iron absorption



binding of iron and calcium (Figure 13.3). This relationship explains some of the seemingly conflicting results obtained in studies on the interaction between calcium and iron (*44*).

For unknown reasons, the addition of soya to a meal reduces the fraction of iron absorbed (*45–48*). This inhibition is not solely explained by the high phytate content of soya. However, because of the high iron content of soya, the net effect on iron absorption with an addition of soya products to a meal is usually positive. In infant foods containing soya, the inhibiting effect can be overcome by the addition of sufficient amounts of ascorbic acid. Conversely, some fermented soy sauces have been found to enhance iron absorption (*49*, *50*).

13.2.6 Enhancement of iron absorption

Ascorbic acid is the most potent enhancer of non-haem iron absorption (*34*, *51–53*). Synthetic vitamin C increases the absorption of iron to the same extent as the native ascorbic acid in fruits, vegetables, and juices. The effect of ascorbic acid on iron absorption is so marked and essential that this effect could be considered as one of vitamin C's physiological roles (*54*). Each meal should preferably contain at least 25 mg of ascorbic acid and possibly more if the meal contains many inhibitors of iron absorption. Therefore, ascorbic acid's role

in iron absorption should be taken into account when establishing the requirements for vitamin C, which currently are set only to prevent vitamin C deficiency (especially scurvy). (See Chapter 7.)

Meat, fish, and seafood all promote the absorption of non-haem iron (*55–58*). The mechanism for this effect has not been determined. It should be pointed out that meat also enhances the absorption of haem iron to about the same extent (*21*). Meat thus promotes iron nutrition in two ways: it stimulates the absorption of both haem and non-haem iron and it provides the well-absorbed haem iron. Epidemiologically, the intake of meat has been found to be associated with a lower prevalence of iron deficiency.

Organic acids, such as citric acid, have been found to enhance the absorption of non-haem iron in some studies (*29*). This effect is not observed as consistently as is that of ascorbic acid (*47*, *52*). Sauerkraut (*59*) and other fermented vegetables and even some fermented soy sauces (*49*, *50*) enhance iron absorption. However, the nature of this enhancement has not yet been determined.

13.2.7 Iron absorption from meals

The pool concept in iron absorption implies that there are two main pools in the gastrointestinal lumen—one pool of haem iron and another pool of non-haem iron—and that iron absorption takes place independently from each pool (*24*). The pool concept also implies that the absorption of iron from the non-haem iron pool is a function of all the ligands present in the mixture of foods included in a meal. The absorption of non-haem iron from a certain meal not only depends on its iron content but also, and to a marked degree, on the composition of the meal (i.e. the balance among all factors enhancing and inhibiting the absorption of iron). The bioavailability can vary more than 10-fold in meals with similar contents of iron, energy, protein, and fat (*20*). The simple addition of certain spices (e.g. oregano) to a meal or the intake of a cup of tea with a meal may reduce the bioavailability by one half or more. Conversely, the addition of certain vegetables or fruits containing ascorbic acid may double or even triple iron absorption, depending on the other properties of the meal and the amounts of ascorbic acid present.

13.2.8 Iron absorption from the whole diet

There is limited information about the total amount of iron absorbed from the diet because no simple method for measuring iron absorption from the whole diet has been available. Traditionally, it has been measured by chemical balance methods using long balance periods or by determining the haemoglobin regeneration rate in subjects with induced iron deficiency anaemia and a well-controlled diet over a long period of time.

More recently, however, new techniques, based on radioiron tracers, have been developed to measure iron absorption from the whole diet. In the first studies of this type to be conducted, all non-haem iron in all meals over periods of 5–10 days was homogeneously labelled to the same specific activity with an extrinsic inorganic radioiron tracer (*43*, *60*). Haem iron absorption was then estimated. In a further study, haem and non-haem iron were separately labelled with two radioiron tracers as biosynthetically labelled haemoglobin and as an inorganic iron salt (*22*). These studies showed that new information could be obtained, for example, about the average bioavailability of dietary iron in different types of diets, the overall effects of certain factors (e.g. calcium) on iron nutrition, and the regulation of iron absorption in relation to iron status. Iron absorption from the whole diet has been extrapolated from the sum of the absorption of iron from the single meals included in the diet. However, it has been suggested that the iron absorption of single meals may exaggerate the absorption of iron from the whole diet (*61*, *62*), as there is a large variation of absorption between meals. Despite this, studies where all meals in a diet are labelled to the same specific activity (the same amount of radioactivity in each meal per unit iron) show that the sum of iron absorption from a great number of single meals agrees with the total absorption from the diet. One study showed that iron absorption from a single meal was the same when the meal was served in the morning after an overnight fast or at lunch or supper (*63*). The same observation was made in another study when a hamburger meal was served in the morning or 2–4 hours after a breakfast (*42*).

Because the sum of energy expenditure and intake set the limit for the amount of food eaten and for meal size, it is practical to relate the bioavailability of iron in different meals to energy content (i.e. the bioavailable nutrient density). The use of the concept of bioavailable nutrient density is a feasible way to compare bioavailability of iron in different meals, construct menus, and calculate recommended intakes of iron (*64*).

Intake of energy and essential nutrients such as iron was probably considerably higher for early humans than it is today (*65–67*). The fact that low iron intake is associated with a low-energy lifestyle implies that the interaction between different factors influencing iron absorption, will be more critical. For example, the interaction between calcium and iron absorption probably had no importance in the nutrition of early humans, who had a diet with ample amounts of both iron and calcium.

13.2.9 Iron balance and regulation of iron absorption

The body has three unique mechanisms for maintaining iron balance. The first is the continuous reutilization of iron from catabolized erythrocytes in the

body. When an erythrocyte dies after about 120 days, it is usually degraded by the macrophages of the reticular endothelium. The iron is released and delivered to transferrin in the plasma, which brings the iron back to red blood cell precursors in the bone marrow or to other cells in different tissues. Uptake and distribution of iron in the body is regulated by the synthesis of transferrin receptors on the cell surface. This system for internal iron transport not only controls the rate of flow of iron to different tissues according to their needs, but also effectively prevents the appearance of free iron and the formation of free radicals in the circulation.

The second mechanism involves access to the specific storage protein, ferritin. This protein stores iron in periods of relatively low need and releases it to meet excessive iron demands. This iron reservoir is especially important in the third trimester of pregnancy.

The third mechanism involves the regulation of absorption of iron from the intestines; decreasing body iron stores trigger increased iron absorption and increasing iron stores trigger decreased iron absorption. Iron absorption decreases until equilibrium is established between absorption and requirement. For a given diet this regulation of iron absorption, however, can only balance losses up to a certain critical point beyond which iron deficiency will develop (*68*). About half of the basal iron losses are from blood and occur primarily in the gastrointestinal tract. Both these losses and the menstrual iron losses are influenced by the haemoglobin level; during the development of an iron deficiency, menstrual and basal iron losses will successively decrease when the haemoglobin level decreases. In a state of more severe iron deficiency, skin iron losses may also decrease. Iron balance (absorption equals losses) may be present not only in normal subjects but also during iron deficiency and iron overload.

The three main factors that affect iron balance are absorption (intake and bioavailability of iron), losses, and stored amount. The interrelationship among these factors has recently been described in mathematical terms, making it possible to predict, for example, the amount of stored iron when iron losses and bioavailability of dietary iron are known (*69*). In states of increased iron requirement or decreased bioavailability, the regulatory capacity to prevent iron deficiency is limited (*68*). However, the regulatory capacity seems to be extremely good in preventing iron overload in a state of increased dietary iron intake or bioavailability (*69*).

13.3 Iron deficiency

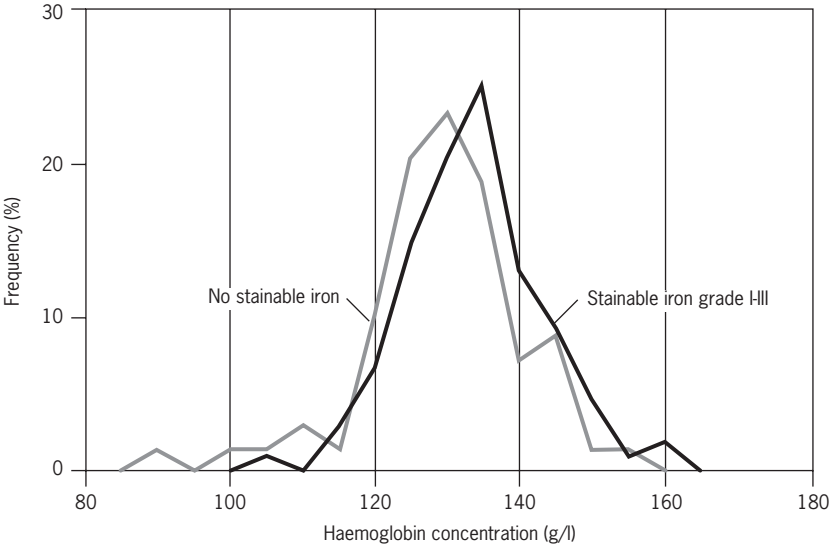
13.3.1 Populations at risk for iron deficiency

Populations most at risk for iron deficiency are infants, children, adolescents, and women of childbearing age, especially pregnant women. The weaning period in infants is especially critical because of the very high iron requirement needed in relation to energy requirement (see section 13.2.2). Thanks to better information about iron deficiency and the addition of fortified cereals to the diets of infants and children, the iron situation has markedly improved in these groups in most developed countries, such that the groups currently considered to be most at risk are menstruating and pregnant women, and adolescents of both sexes. In developing countries, however, the iron situation is still very critical in many groups—especially in infants in the weaning period. During this period, iron nutrition is of great importance for the adequate development of the brain and other tissues such as muscles, which are differentiated early in life.

Iron deficiency and iron deficiency anaemia are often incorrectly used as synonyms. A definition of these terms may clarify some of the confusion about different prevalence figures given in the literature (*70*). Iron deficiency is defined as a haemoglobin concentration below the optimum value in an *individual*, whereas iron deficiency anaemia implies that the haemoglobin concentration is below the 95th percentile of the distribution of haemoglobin concentration in a *population* (disregarding effects of altitude, age and sex, etc. on haemoglobin concentration). The confusion arises due to the very wide distribution of the haemoglobin concentration in healthy, fully iron-replete subjects (in women, 120–160 g/l; in men, 140–180 g/l) (*71*). During the development of a negative iron balance in subjects with no mobilizable iron from iron stores (i.e. no visible iron in technically perfect bone marrow smears or a serum ferritin concentration <15 µg/l), there will be an immediate impairment in the production of haemoglobin with a resulting decrease in haemoglobin and different erythrocyte indexes (e.g. mean corpuscular haemoglobin and mean corpuscular volume). In turn, this will lead to an overlap in the distributions of haemoglobin in iron-deficient and iron-replete women (Figure 13.4). The extent of overlap depends on the prevalence and severity of iron deficiency. In populations with more severe iron deficiency, for example, the overlap is much less marked.

In women, anaemia is defined as a haemoglobin level <120 g/l. For a woman who has her normal homeostatic value set at 150 g/l, her haemoglobin level must decrease by 26% to 119 g/l before she is considered to be anaemic, whereas for a woman who has her normal haemoglobin set at 121 g/l, her haemoglobin level must only decrease by 1.5% to 119 g/l. Iron

FIGURE 13.4
Distribution of haemoglobin concentration in a sample of 38-year-old women with and without stainable bone marrow iron



The main fraction (91%) of the iron-deficient women in this sample had haemoglobin levels above the lowest normal level for the population: 120 g/l (mean ± 2 SD). The degree of overlap of the two distributions depends on the severity of anaemia in a population.
Source: reference (*68*).

deficiency anaemia is a rather imprecise concept for evaluating the single subject and has no immediate physiological meaning. By definition, this implies that the prevalence of iron deficiency anaemia is less frequent than iron deficiency and that the presence of anaemia in a subject is a statistical rather than a functional concept. The main use of the cut-off value in defining anaemia is in comparisons between population groups (*72*). In practical work, iron deficiency anaemia should be replaced by the functional concept of iron deficiency. Anaemia per se is mainly important when it becomes so severe that oxygen delivery to tissues is impaired. An iron deficiency anaemia which develops slowly in otherwise healthy subjects with moderately heavy work output will not give any symptoms until the haemoglobin level is about 80 g/l or lower (*71*). The reason for the continued use of the concept of iron deficiency anaemia is the ease of determining haemoglobin. Therefore, in clinical practice, knowledge of previous haemoglobin values in a subject is of great importance for evaluating the diagnosis.

Iron deficiency being defined as an absence of iron stores combined with signs of an iron-deficient erythropoiesis implies that in a state of iron defi-

ciency there is an insufficient supply of iron to various tissues. This occurs at a serum ferritin level <15 µg/l. At this point, insufficient amounts of iron will be delivered to transferrin, the circulating transport protein for iron, and the binding sites for iron on transferrin will therefore contain less and less iron. This is usually described as a reduction in transferrin saturation. When transferrin saturation drops to a certain critical level, erythrocyte precursors, which continuously need iron for the formation of haemoglobin, will get an insufficient supply of iron. At the same time, the supply of iron by transferrin to other tissues will also be impaired. Liver cells will get less iron, more transferrin will be synthesized, and the concentration of transferrin in plasma will then suddenly increase. Cells with a high turnover rate are the first ones to be affected (e.g. intestinal mucosal cells with a short lifespan). The iron–transferrin complex binds to transferrin receptors on certain cell surfaces and is then taken up by invagination of the whole complex on the cell wall. The uptake of iron seems to be related both to transferrin saturation and the number of transferrin receptors on the cell surface (*73*, *74*). There is a marked diurnal variation in the saturation of transferrin because the turnover rate of iron in plasma is very high. This fact makes it difficult to evaluate the iron status from single determinations of transferrin saturation.

13.3.2 Indicators of iron deficiency

The absence of iron stores (iron deficiency) can be diagnosed by showing that there is no stainable iron in the reticuloendothelial cells in bone marrow smears or, more easily, by a low concentration of ferritin in serum (<15 µg/l). Even if an absence of iron stores per se may not necessarily be associated with any immediate adverse effects, it is a reliable and good indirect indicator of iron-deficient erythropoiesis and of an increased risk of a compromised supply of iron to different tissues.

Even before iron stores are completely exhausted, the supply of iron to the erythrocyte precursors in the bone marrow is compromised, leading to iron-deficient erythropoiesis (*70*). A possible explanation is that the rate of release of iron from stores is influenced by the amount of iron remaining. As mentioned above, it can then be assumed that the supply of iron to other tissues needing iron is also insufficient because the identical transport system is used. During the development of iron deficiency haemoglobin concentration, transferrin concentration, transferrin saturation, transferrin receptors in plasma, erythrocyte protoporphyrin, and erythrocyte indexes are changed. All these indicators, however, show a marked overlap between normal and iron-deficient subjects, which makes it impossible to identify the single subject with mild iron deficiency by looking at any single one of these indicators.

Therefore, these tests are generally used in combination (e.g. for interpreting results from the second National Health and Nutrition Examination Survey in the United States [*75*, *76*]). By increasing the number of tests used, the diagnostic specificity then increases but the sensitivity decreases, and thus the true prevalence of iron deficiency is markedly underestimated if multiple diagnostic criteria are used. Fortunately, a low serum ferritin (<15 µg/l) is always associated with an iron-deficient erythropoiesis. The use of serum ferritin alone as a measure will also underestimate the true prevalence of iron deficiency but to a lesser degree than when the combined criteria are used.

A diagnosis of iron deficiency anaemia can be suspected if anaemia is present in subjects who are iron-deficient as described above. Preferably, to fully establish the diagnosis, the subjects should respond adequately to iron treatment. The pitfalls with this method are the random variation in haemoglobin concentrations over time and the effect of the regression towards the mean when a new measurement is made.

The use of serum ferritin has improved the diagnostic accuracy of iron deficiency. It is the only simple method available to detect early iron deficiency. Its practical value is somewhat reduced, however, by the fact that serum ferritin is a very sensitive acute-phase reactant and may be increased for weeks after a simple infection with fever for a day or two (*77*). Several other conditions, such as use of alcohol (*78*, *79*), liver disease, and collagen diseases, may also increase serum ferritin concentrations. Determination of transferrin receptors in plasma has also been recommended in the diagnosis of iron deficiency. The advantage of this procedure is that it is not influenced by infections. Its main use is in subjects who are already anaemic and it is not sensitive enough for the early diagnosis of iron deficiency. The use of a combination of determinations of serum ferritin and serum transferrin receptors has also been suggested (*80*).

13.3.3 Causes of iron deficiency

Nutritional iron deficiency implies that the diet cannot supply enough iron to cover the body's physiological requirements for this mineral. Worldwide this is the most common cause of iron deficiency. In many tropical countries, infestations with hookworms lead to intestinal blood losses that in some individuals can be considerable. The average blood loss can be reliably estimated by egg counts in stools. Usually the diet in these populations is also limited with respect to iron content and availability. The severity of the infestations varies markedly between subjects and regions.

In clinical practice, a diagnosis of iron deficiency must always lead to a search for pathologic causes of blood loss (e.g. tumours in the gastrointesti-

nal tract or uterus, especially if uterine bleedings have increased or changed in regularity). Patients with achlorhydria absorb dietary iron less well (a reduction of about 50%) than healthy individuals, and patients who have undergone gastric surgery, especially if the surgery was extensive, may eventually develop iron deficiency because of impaired iron absorption. Gluten enteropathy is another possibility to consider, especially in young patients.

13.3.4 Prevalence of iron deficiency

Iron deficiency is probably the most common nutritional deficiency disorder in the world. A recent estimate based on WHO criteria indicated that around 600–700 million people worldwide have marked iron deficiency anaemia (*81*), and the bulk of these people live in developing countries. In developed countries, the prevalence of iron deficiency anaemia is much lower and usually varies between 2% and 8%. However, the prevalence of iron deficiency, including both anaemic and non-anaemic subjects (see definitions above), is much higher. In developed countries, for example, an absence of iron stores or subnormal serum ferritin values is found in about 20–30% of women of fertile age. In adolescent girls, the prevalence is even higher.

It is difficult to determine the prevalence of iron deficiency more exactly because representative populations for clinical investigation are hard to obtain. Laboratory methods and techniques for blood sampling need careful standardization. One often neglected source of error (e.g. when samples from different regions, or samples taken at different times, are compared) comes from the use of reagent kits for determining serum ferritin that are not adequately calibrated to international WHO standards. In addition, seasonal variations in infection rates influence the sensitivity and specificity of most methods used.

Worldwide, the highest prevalence figures for iron deficiency are found in infants, children, adolescents, and women of childbearing age. Both better information about iron deficiency prevention and increased consumption of fortified cereals by infants and children have markedly improved the iron situation in these groups in most developed countries, such that, the highest prevalence of iron deficiency today is observed in menstruating and pregnant women, and adolescents of both sexes.

In developing countries, where the prevalence of iron deficiency is very high and the severity of anaemia is marked, studies on the distribution of haemoglobin in different population groups can provide important information that can then be used as a basis for action programmes (*72*). A more detailed analysis of subsamples may then give excellent information for the planning of more extensive programmes.

13.3.5 Effects of iron deficiency

Studies in animals have clearly shown that iron deficiency has several negative effects on important functions in the body (*3*). The physical working capacity of rats is significantly reduced in states of iron deficiency, especially during endurance activities (*82*, *83*). This negative effect seems to be less related to the degree of anaemia than to impaired oxidative metabolism in the muscles with an increased formation of lactic acid. Thus, the effect witnessed seems to be due to a lack of iron-containing enzymes which are rate limiting for oxidative metabolism (*84*). Further to this, several groups have observed a reduction in physical working capacity in human populations with long-standing iron deficiency, and demonstrated an improvement in working capacity in these populations after iron administration (*84*).

The relationship between iron deficiency and brain function and development is very important to consider when choosing a strategy to combat iron deficiency (*85–88*). Several structures in the brain have a high iron content; levels are of the same order of magnitude as those observed in the liver. The observation that the lower iron content of the brain in iron-deficient growing rats cannot be increased by giving iron at a later date strongly suggests that the supply of iron to brain cells takes place during an early phase of brain development and that, as such, early iron deficiency may lead to irreparable damage to brain cells. In humans about 10% of brain-iron is present at birth; at the age of 10 years the brain has only reached half its normal iron content, and optimal amounts are first reached between the ages of 20 and 30 years.

Iron deficiency also negatively influences the normal defence systems against infections. In animal studies, the cell-mediated immunologic response by the action of T-lymphocytes is impaired as a result of a reduced formation of these cells. This in turn is due to a reduced DNA synthesis dependent on the function of ribonucleotide reductase, which requires a continuous supply of iron for its function. In addition, the phagocytosis and killing of bacteria by the neutrophil leukocytes is an important component of the defence mechanism against infections. These functions are impaired in iron deficiency as well. The killing function is based on the formation of free hydroxyl radicals within the leukocytes, the respiratory burst, and results from the activation of the iron-sulfur enzyme NADPH oxidase and probably also cytochrome b (a haem enzyme) (*89*).

The impairment of the immunologic defence against infections that was found in animals is also regularly found in humans. Administration of iron normalizes these changes within 4–7 days. It has been difficult to demonstrate, however, that the prevalence of infections is higher or that their severity is

more marked in iron-deficient subjects than in control subjects. This may well be ascribed to the difficulty in studying this problem with an adequate experimental design.

Several groups have demonstrated a relationship between iron deficiency and attention, memory, and learning in infants and small children. In the most recent well-controlled studies, no effect was noted from the administration of iron. This finding is consistent with the observations in animals. Therapy-resistant behavioural impairment and the fact that there is an accumulation of iron during the whole period of brain growth should be considered strong arguments for the early detection and treatment of iron deficiency. This is valid for women, especially during pregnancy, and for infants and children, up through the period of adolescence to adulthood. In a recent well-controlled study, administration of iron to non-anaemic but iron-deficient adolescent girls improved verbal learning and memory (*90*).

Well-controlled studies in adolescent girls show that iron-deficiency without anaemia is associated with reduced physical endurance (*91*) and changes in mood and ability to concentrate (*92*). Another recent study showed that there was a reduction in maximum oxygen consumption in non-anaemic women with iron deficiency that was unrelated to a decreased oxygen-transport capacity of the blood (*93*).

13.4 Iron requirements during pregnancy and lactation

Iron requirements during pregnancy are well established (Table 13.2). Most of the iron required during pregnancy is used to increase the haemoglobin mass of the mother; this increase occurs in all healthy pregnant women who

TABLE 13.2
Iron requirements during pregnancy

	Iron requirements (mg)
Iron requirements during pregnancy	
Fetus	300
Placenta	50
Expansion of maternal erythrocyte mass	450
Basal iron losses	240
Total iron requirement	**1040**
Net iron balance after delivery	
Contraction of maternal erythrocyte mass	+450
Maternal blood loss	–250
Net iron balance	**+200**
Net iron requirements for pregnancy[a]	**840**

[a] Assuming sufficient material iron stores are present.

have sufficiently large iron stores or who are adequately supplemented with iron. The increased haemoglobin mass is directly proportional to the increased need for oxygen transport during pregnancy and is one of the important physiological adaptations that occurs in pregnancy (*94*, *95*). A major problem in maintaining iron balance in pregnancy is that iron requirements are not equally distributed over its duration. The exponential growth of the fetus in the last trimester of pregnancy means that more than 80% of fetal iron needs relate to this period. The total daily iron requirements, including the basal iron losses (0.8 mg), increase during pregnancy from 0.8 mg to about 10 mg during the last 6 weeks of pregnancy.

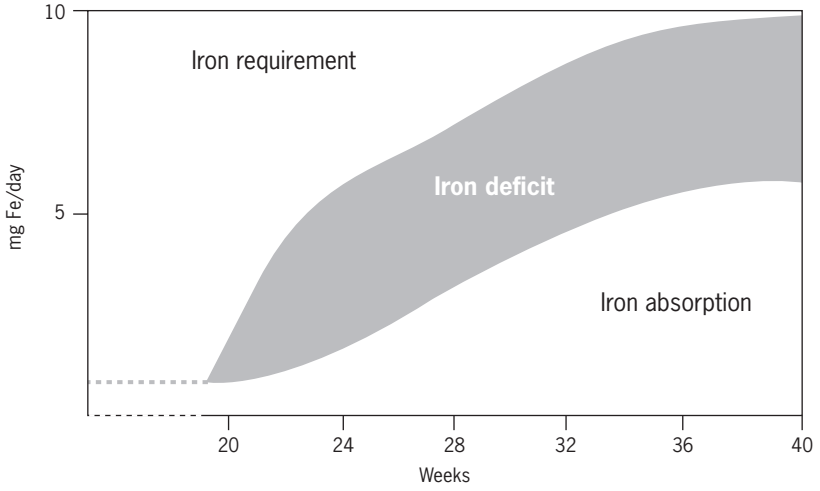
In lactating women, the daily iron loss in milk is about 0.3 mg. Together with the basal iron losses of 0.8 mg, the total iron requirements during the lactation period amount to 1.1 mg/day.

Iron absorption during pregnancy is determined by the amount of iron in the diet, its bioavailability (meal composition), and the changes in iron absorption that occur during pregnancy. There are marked changes in the fraction of iron absorbed during pregnancy. In the first trimester, there is a marked, somewhat paradoxical, decrease in the absorption of iron, which is closely related to the reduction in iron requirements during this period as compared with the non-pregnant state (see below). In the second trimester, iron absorption is increased by about 50%, and in the last trimester it may increase by up to about four times the norm. Even considering the marked increase in iron absorption, it is impossible for the mother to cover her iron requirements from diet alone, even if her diet's iron content and bioavailability are very high. In diets prevailing in most developed countries, there will be a deficit of about 400–500 mg in the amount of iron absorbed versus required during pregnancy (Figure 13.5).

An adequate iron balance can be achieved if iron stores of 500 mg are available during the second and third trimesters. However, it is uncommon for women today to have iron stores of this size. It is therefore recommended that iron supplements in tablet form, preferably together with folic acid, be given to all pregnant women because of the difficulties in correctly evaluating iron status in pregnancy with routine laboratory methods. In the non-anaemic pregnant woman, daily supplements of 100 mg of iron (e.g. as ferrous sulphate) given during the second half of pregnancy are adequate. In anaemic women, higher doses are usually required.

During the birth process, the average blood loss corresponds to about 250 mg iron. At the same time, however, the haemoglobin mass of the mother gradually normalizes, which implies that about 200 mg iron from the expanded haemoglobin mass (150–250 mg) is returned to the mother. To cover

FIGURE 13.5
Daily iron requirements and daily dietary iron absorption in pregnancy



The shaded area represents the deficit of iron that has to be covered by iron from stores or iron supplementation.

the needs of a woman after pregnancy, a further 300 mg of iron must be accumulated in the iron stores in order for the woman to start her next pregnancy with about 500 mg of stored iron; such restitution is not possible with present types of diets.

There is an association between low haemoglobin values and premature birth. An extensive study (*96*) showed that a woman with a haematocrit of 37% had twice the risk of having a premature birth, as did a woman with a haematocrit between 41% and 44% ($P \leq 0.01$). A similar observation was reported in another extensive study in the United States (*97*). The subjects were examined retrospectively and the cause of the lower haematocrit was not investigated.

Early in pregnancy there are marked hormonal, haemodynamic, and haematologic changes. There is, for example, a very early increase in the plasma volume, which has been used to explain the physiological anaemia of pregnancy observed in iron-replete women. The primary cause of this phenomenon, however, is more probably an increased ability of the haemoglobin to deliver oxygen to the tissues (fetus). This change is induced early in pregnancy by increasing the content of 2,3-diphospho-D-glycerate in the erythrocytes, which shifts the haemoglobin–oxygen dissociation curve to the right. The anaemia is a consequence of this important adaptation and it is not

primarily a desirable change, for example, to improve placental blood flow by reducing blood viscosity.

Another observation has similarly caused some confusion about the rationale of giving extra iron routinely in pregnancy. In extensive studies of pregnant women, a U-shaped relationship between various pregnancy complications and the haemoglobin level has been noted (i.e. there are more complications at both low and high levels). There is nothing to indicate, however, that high haemoglobin levels (within the normal non-pregnant range) per se have any negative effects. The haemoglobin increase is caused by pathologic hormonal and haemodynamic changes induced by an increased sensitivity to angiotensin II, which occurs in some pregnant women, leading to a reduction in plasma volume, hypertension, and toxaemia of pregnancy.

Pregnancy in adolescents presents a special problem because iron is needed to cover the requirements of growth for the mother and the fetus. In countries with very early marriage, a girl may get pregnant before menstruating. The combined iron requirements for growth and pregnancy are very high and the iron situation is very serious for these adolescents.

In summary, the physiological adjustments occurring in pregnancy are not sufficient to balance its very marked iron requirements, and the pregnant woman has to rely on her iron stores. In developed countries, the composition of the diet has not been adjusted to the present low-energy-demanding lifestyles found there. As a result, women in these countries have insufficient or empty iron stores during pregnancy. This is probably the main cause of the critical iron-balance situation in pregnant women in these countries today. The unnatural necessity to give extra nutrients such as iron and folate to otherwise healthy pregnant women should be considered in this perspective.

13.5 Iron supplementation and fortification

The prevention of iron deficiency has become more urgent in recent years with the accumulation of evidence strongly suggesting a relationship between even mild iron deficiency and impaired brain development, and especially so in view of the observation that functional defects affecting learning and behaviour cannot be reversed by giving iron at a later date. As mentioned, iron deficiency is common both in developed and in developing countries. Great efforts have been made by WHO to develop methods to combat iron deficiency.

Iron deficiency can generally be combated by one or more of the following three strategies: (1) iron supplementation (i.e. giving iron tablets to certain target groups such as pregnant women and preschool children); (2) iron fortification of certain foods, such as flour; and (3) food and nutrition education

on improving the amount of iron absorbed from the diet by increasing the intake of iron and especially by improving the bioavailability of the dietary iron.

Several factors determine the feasibility and effectiveness of different strategies, such as the health infrastructure of a society, the economy, and access to suitable methods of iron fortification. The solutions are therefore often quite different in developing and developed countries. There is a need to obtain new knowledge about the feasibility of different methods to improve iron nutrition and to apply present knowledge in more effective ways. Further to this, initiation of local activities on the issue of iron nutrition should be stimulated while actions from governments are awaited.

13.6 Evidence used for estimating recommended nutrient intakes

To translate physiological iron requirements, given in Table 13.1, into dietary iron requirements, the bioavailability of iron in different diets must be calculated. It is also necessary to define an iron status where the supply of iron to the erythrocyte precursors and other tissues begins to be compromised. A state of iron-deficient erythropoiesis occurs when iron can no longer be mobilized from iron stores; iron can no longer be mobilized when stores are almost completely empty. A reduction then occurs, for example, in the concentration of haemoglobin and in the average content of haemoglobin in the erythrocytes (i.e. a reduction in mean corpuscular haemoglobin). At the same time the concentration of transferrin in the plasma increases because of an insufficient supply of iron to liver cells. These changes were recently shown to occur rather suddenly at a level of serum ferritin <15 µg/l (*68*, *70*). A continued negative iron balance will further reduce the level of haemoglobin. Symptoms related to iron deficiency are less related to the haemoglobin level and more to the fact that there is a compromised supply of iron to tissues.

The bioavailability of iron in meals consumed in countries with a Western-type diet has been measured by using different methods. Numerous single-meal studies have shown absorption of non-haem iron ranging from 5% to 40% (*59*, *98*, *99*). Attempts have also been made to estimate the bioavailability of dietary iron in populations consuming Western-type diets by using indirect methods (e.g. calculation of the coverage of iron requirements in groups of subjects with known dietary intake). Such studies suggest that in borderline iron-deficient subjects, the bioavailability from healthy diets may reach a level of around 14–16% (15% relates to subjects who have a serum ferritin value of <15 µg/l or a reference dose absorption of 56.5%) (*19*).

New radioiron tracer techniques have enabled direct measurements of the

average bioavailability of iron in different Western-type diets to be made (*22*, *43*, *60*). Expressed as total amounts of iron absorbed from the whole diet, it was found that 53.2 µg/kg/day could be absorbed daily from each of the two main meals of an experimental diet which included ample amounts of meat or fish. For a body weight of 55 kg and an iron intake of 14 mg/day, this corresponds to a bioavailability of 21% in subjects with no iron stores and an iron-deficient erythropoiesis. A diet common among women in Sweden containing smaller portions of meat and fish, higher amounts of phytate-containing foods, and some vegetarian meals each week was found to have a bioavailability of 12%. Reducing the intake of meat and fish further reduced the bioavailability to about 10% (25 µg Fe/kg/day).

In vegetarians, the bioavailability of iron is usually low because of the absence of meat and fish and a high intake of foods containing phytates and polyphenols. A Western-type diet that includes servings of fruits and vegetables, along with meat and fish has a bioavailability of about 15%, but for the typical Western-type diet—especially among women—the bioavailability is around 12% or even 10%. In countries or for certain groups in a population with a very high meat intake, the bioavailability may be around 18%. In the more developed countries, a high bioavailability of iron from the diet is mainly associated with a high meat intake, a high intake of ascorbic acid with meals, a low intake of phytate-rich cereals, and no coffee or tea within 2 hours of the main meals (*38*). Table 13.3 shows examples of diets with different iron bioavailability. Table 13.4 shows the bioavailability of iron for two levels of iron intake in a 55-kg woman with no iron stores.

Iron absorption data are also available from several population groups in Africa (*100*), South America (*101*), India (*102*), and south-east (*103–107*) Asia. The bioavailability of different Indian diets, after an adjustment to a reference dose absorption of 56.5%, was 1.7–1.8% for millet-based diets, 3.5–4.0% for

TABLE 13.3
Examples of diets with different iron bioavailability

Type of diet	Bioavailability (µg/kg/day)
Very high meat in two main meals daily and high ascorbic acid (theoretical)	75.0
High meat/fish in two main meals daily	66.7
Moderate meat/fish in two main meals daily	53.2
Moderate meat/fish in two main meals daily; low phytate and calcium	42.3
Meat/fish in 60% of two main meals daily; high phytate and calcium	31.4
Low meat intake; high phytate; often one main meal	25.0
Meat/fish negligible; high phytate; high tannin and low ascorbic acid	15.0
Pre-agricultural ancestors	
Plant/animal subsistence: 65/35; *very* high meat and ascorbic acid intake	150

TABLE 13.4
Translation of bioavailability (expressed as amount of iron absorbed) into percentage absorbed for two levels of iron intake (15 and 17 mg/day)

Bioavailability (µg/kg/day)	Absorption in a 55-kg woman with no iron stores (mg/day)	Bioavailability (%)	
		15 mg/day	17 mg/day
150	8.25	55.0	48.8
75.0	4.13	27.5	24.4
66.7	3.67	24.5	21.8
53.2	2.93	19.5	17.0
42.3	2.32	15.5	13.5
31.4	1.73	11.5	10.0
25.0	1.38	9.2	8.2
15.0	0.83	5.5	4.7

wheat-based diets, and 8.3–10.3% for rice-based diets (*102*). In south-east Asia, iron absorption data has been reported from Burma and Thailand. In Burma, iron absorption from a basal rice-based meal was 1.7%; when the meal contained 15 g of fish the bioavailability of iron was 5.5%, and with 40 g of fish, it was 10.1% (*103*). In Thailand, iron absorption from a basal rice-based meal was 1.9%; adding 100 g of fresh fruit increased absorption to 4.8% and adding 80 g of lean meat increased non-haem iron absorption to 5.4% (*104*, *105*). In three other studies where basal meals included servings of vegetables rich in ascorbic acid, the absorption figures were 5.9%, 10.0%, and 10.8%, respectively (*106*). In a further study in Thailand, 60 g of fish were added to the same basal meal, which increased absorption to 21.6% (*106*). Another such study in central Thailand examined the reproducibility of dietary iron absorption measurements under optimal field conditions for 20 farmers and labourers (16 men, 4 women). The subjects had a free choice of foods (i.e. rice, vegetables, soup, a curry, and a fish dish). All foods consumed were weighed and the rice was labelled with an extrinsic radioiron tracer. The mean absorption of iron was 20.3% (adjusted to reference dose absorption of 56.5%) (*107*).

It is obvious that absorbed iron requirements need to be adjusted to different types of diets, especially in vulnerable groups. In setting recommended intakes in the 1980s FAO and WHO proposed, for didactic reasons, the use of three bioavailability levels, 5%, 10%, and 15% (*8*). In light of more recent studies discussed herein, for developing countries, it may be more realistic to use the figures of 5% and 10%. In populations consuming more Western-type diets, two levels would be appropriate—12% and 15%—depending mainly on meat intake.

The amount of dietary iron absorbed is mainly determined by the amount of body stores of iron and by the properties of the diet (iron content and bioavailability). (In anaemic subjects, the rate of erythrocyte production also

influences iron absorption.) For example, in a 55-kg woman with average iron losses who consumes a diet with an iron bioavailability of 15%, the mean iron stores would be about 120 mg. Furthermore, approximately 10–15% of women consuming this diet would have no iron stores. In a 55-kg woman who consumes a diet with an iron bioavailability of 12%, iron stores would be approximately 75 mg and about 25–30% of women consuming this diet would have no iron stores. When the bioavailability of iron decreases to 10%, mean iron stores are reduced to about 25 mg, and about 40–50% of women consuming this diet would have no iron stores. Women consuming diets with an iron bioavailability of 5% have no iron stores and they are iron deficient.

13.7 Recommendations for iron intakes

The recommended nutrient intakes (RNIs) for varying dietary iron bioavailabilities are shown in Table 13.5. The RNIs are based on the 95th percentile of the absorbed iron requirements (Table 13.1). No figures are given for dietary iron requirements in pregnant women because the iron balance in pregnancy depends not only on the properties of the diet but also and especially on the amounts of stored iron.

TABLE 13.5
The recommended nutrient intakes (RNIs) for iron for different dietary iron bioavailabilities (mg/day)

Group	Age (years)	Mean body weight (kg)	Recommended nutrient intake (mg/day) for a dietary iron bioavailability of			
			15%	12%	10%	5%
Infants and children	0.5–1	9	6.2[a]	7.7[a]	9.3[a]	18.6[a]
	1–3	13	3.9	4.8	5.8	11.6
	4–6	19	4.2	5.3	6.3	12.6
	7–10	28	5.9	7.4	8.9	17.8
Males	11–14	45	9.7	12.2	14.6	29.2
	15–17	64	12.5	15.7	18.8	37.6
	18+	75	9.1	11.4	13.7	27.4
Females	11–14[b]	46	9.3	11.7	14.0	28.0
	11–14	46	21.8	27.7	32.7	65.4
	15–17	56	20.7	25.8	31.0	62.0
	18+	62	19.6	24.5	29.4	58.8
Postmenopausal		62	7.5	9.4	11.3	22.6
Lactating		62	10.0	12.5	15.0	30.0

[a] Bioavailability of dietary iron during this period varies greatly.
[b] Pre-menarche.
Source: adapted, in part, from reference (*8*) and in part on new calculations of the distribution of iron requirements in menstruating women. Because of the very skewed distribution of iron requirements in these women, dietary iron requirements are calculated for four levels of dietary iron bioavailability.

13.8 Recommendations for future research

The following were identified as priority areas for future research efforts:

- Acquire knowledge of the content of phytate and iron-binding polyphenols in food, condiments, and spices and produce new food tables which include such data.
- Acquire knowledge about detailed composition of common meals in different regions of the world and their usual variation in composition to examine the feasibility of making realistic recommendations about changes in meal composition, taking into consideration the effect of such changes on other nutrients (e.g. vitamin A).
- Give high priority to systematic research in the area of iron requirements. The very high iron requirements, especially in relation to energy requirements, in the weaning period make it difficult to develop appropriate diets based on recommendations that are effective and realistic. Alternatives such as home fortification of weaning foods should also be considered.
- Critically analyse the effectiveness of iron compounds used for fortification.
- Study models for improving iron supplementation—from the distribution of iron tablets to increasing the motivation of individuals to take iron supplements, especially during pregnancy.

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