

## Chapter 9 Nutritional Anaemia

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Nutritional anemias comprise the second most common group of deficiency disorders after protein-energy malnutrition. Nutritional anemia is defined as anaemia which occurs when there is a deficiency of one or more of the essential nutrients required for the synthesis of haemoglobin and the production of erythrocytes. Several nutrients are required for erythropoiesis.

Iron, folic acid, vitamin B<sub>12</sub>, protein, pyridoxine, vitamin C, copper and possibly vitamin E are all necessary for the proper function of the bone marrow. Iron is an essential component of haemoglobin and a large proportion of nutritional anaemia in the world is caused by its deficiency. Iron deficiency tends to be most common when the intake is not enough to meet the demands of growth, e.g. in pregnancy, during infancy and at adolescence. Infections and parasitic infestations are also important; they may interfere with the activity of the marrow, or increase erythropoiesis by causing blood loss or haemolysis. Iron deficiency also occurs in malabsorption syndromes.

Anaemia due to deficiency of folic acid and vitamin B<sub>12</sub> is much less common. Both folic acid and B<sub>12</sub> play a key role in cellular metabolism and are needed for the normal development of the erythrocytes in the bone marrow. Folic acid deficiency is more common than that of vitamin B<sub>12</sub>, and is mostly seen during pregnancy, when the demands of the fetus are added to those of the mother. Apart from pregnancy, deficiencies of folic acid and B<sub>12</sub> are rare except in malabsorption and in certain diseases of the bowel as, for example, tropical sprue.

## PREVALENCE

Anemia is a common cause of hospital admissions in infants and young children in most of the developing world. In some countries of tropical Africa up to 4 per cent of paediatric admissions are for anaemia, a figure equivalent to that for admissions due to protein-energy malnutrition; the mortality from anaemia can be as high as 9-10 per cent. The frequency of anaemia in out-patients is even higher. Of 5000 patients attending the teaching hospital in Dares-Salaam, the mean haemoglobin value amongst 2539 men was 8.85 g/100 ml. Among 2108 women it was 7.86 g/100 ml, and in 853 children in the age group 1-5 years it was 6.78 g/100 ml. In Mauritius, anaemia is the second most important cause of admissions to hospital and in Sierra Leone up to 40 per cent of adult females suffer from it.

Community studies have been few and scattered. In one detailed study spread over seven countries of South America it was found that iron deficiency occurred in 48 per cent of pregnant women as compared with 21 per cent non-pregnant women, and in 3 per cent of the males of the same age groups. Anaemia, defined as haemoglobin less than 11 g/100 ml, was found in 38.5 per cent of pregnant women, 17.3 per cent of non-pregnant women and 3.9 per cent of men. The prevalence of folic acid and vitamin B<sub>12</sub> deficiency was much lower and these deficiencies seemed to occur only during pregnancy.

In the Gambia, in one longitudinal study, 473 rural children under the age of 5 years were examined at intervals of 3 months for a period of 26 months. In that community the common practice is to breast feed all children exclusively for 4-6 months, after which cereal pap is introduced and gradually supplemented with sauces of fish, ground nuts or green leaves and boiled rice. The mean haemoglobin value under the age of 1 month was found to be 15.4 g/100 ml. It fell as the children grew older, reaching 9.0 g/100 ml at the age of 15-24 months, after which there was a slow improvement. These values are lower than those of poor Aberdeen children quoted below. A well-marked seasonal cycle was observed in the Gambia. There was a sharp decline in haemoglobin values in the latter part of the wet season, indicating that malaria is a key aetiological factor in this

age group. In another study of anaemia in rural women in the Gambia a high frequency of iron deficiency was observed. In this group there was a strong association between anaemia and three independent variables- pregnancy, heavy menstrual bleeding and splenomegaly.

A cross-sectional study of haemoglobin values in 726 children under the age of 5 years in several coastal villages in Tanzania showed that anaemia was as common as in the Gambia. The mean haemoglobin was 8.3 g/100 ml in the first 6 months of life, increasing slowly to reach a mean of 9.2 g/100 ml between the ages of 5 and 6 years. Again malaria appeared to be implicated. For example, in the city of Dares-Salaam, where malaria transmission is considerably less, the mean haemoglobin values were higher - 10 g/100 ml in the age group 5-6 years.

Forty infants under the age of 6 months with severe anaemia were studied in Dares-Salaam. Apart from six who suffered from sickle cell anaemia, all had iron deficiency with little or no iron stores in the bone marrow. A large majority were born to mothers who had received no antenatal care during pregnancy. It was thought that many of these infants were born with poor iron stores and could not cope with the requirements of growth. Episodes of malaria made the existing deficiency worse and precipitated acute anaemia.

Collaborative studies under the auspices of the World Health Organization indicate that nutritional anaemia affects between 10 and 20 per cent of the populations of the developing countries. The most common cause is iron deficiency, but often deficiencies of folic acid and B12 are also simultaneously present, especially in pregnant women (table 9.1).

**Table 9.1 Prevalence of nutritional anaemia in the developing world**

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*Africa*

- 6-17 % adult males.
- 15-50 % adult females.
- 35- 72 % pregnant women
- 30-60% children under the age of 15 years.

*Asia*

- 10 % adult males.
- 30-50 % adult females. The rates are higher amongst pregnant women reaching 37 – 75 % in certain regions of India, Pakistan and Bangladesh.
- 50% children. The rates are higher in children under the age of 2 years.

*Central and South America*

5-15 % adult males.

10-35 % adult females. The rates are higher, 37- 52 % amongst pregnant women.

15-50% infants.

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Such cross-sectional data are becoming available for many communities, indicating the extensive prevalence of anaemia. Even though there are no symptoms from the anaemia it does contribute to ill-health and reduces productivity. In malarious areas, control measures result in better average levels of haemoglobin. This was the experience in Tanzania after instituting control measures. Also community surveys in India, where malaria eradication programmes have been in operation since the 1960s, show higher haemoglobin levels compared to communities where malaria is holo-endemic. A cross-sectional study in 544 rural Punjabi children showed a mean haemoglobin level of 11.0 g/100 ml under the age of 6 months, falling to 9.2 g/100 ml at age 18-24 months and rising again to 10.5 g/100 ml at 3 years.

In malaria endemic regions severe anaemia is commonly encountered. Twenty-six studies on haemoglobin levels in pregnant women in sub-Saharan Africa could be matched with the intensity of transmission of malaria as gauged by parasite ratio in children <15 years old which provides a good measure of transmission. In areas with no malaria the mean haemoglobin levels were higher than those found in areas with stable malaria transmission. It has been estimated that as many as 400 000 pregnant women develop severe anaemia annually as a result of severe infection in sub-Saharan Africa.

In many affluent societies of Western Europe nutritional anaemia used to be a major public health problem until quite recently. In 1935 a survey of 3500 individuals from the poorer classes in Aberdeen showed that between the ages of 5 and 23 months the frequency of anaemia was 41 per cent and in 7 per cent the haemoglobin level was less than 10.2 g/100 ml. Between the ages of 2 and 5 years, 32 per cent had haemoglobin levels below 11 g/100 ml. After this age slow improvement occurred until adolescence when, amongst 246 pubertal girls, 1 per cent had haemoglobin levels below 9.6 g/100 ml. Anaemia was not a problem among adult men; women tended to have lower haemoglobin values, especially during pregnancy when 17.5 per cent showed values of less than 9.6 g/100 ml. Thus, three age groups were identified as being at risk; viz. infancy, adolescence especially in girls, and pregnancy. Since then there has been a marked improvement. Recently a mean haemoglobin value of 11.0 g/100 ml has been recorded in Bristol children between the ages of 3 and 24 months and in Cardiff children a mean value of 12.0 g/100 ml in the second year rising to 12.4 g/100 ml at 5 years has been reported.

The general improvements in diet and in health standards have largely contributed to the falling incidence of anaemia in British children. A similar improvement has also been found in pregnant women since 1940, though early prophylaxis with iron and folic acid has also been responsible for the fall in the incidence of anaemia of pregnancy.

## AETIOLOGICAL FACTORS

### Iron deficiency

Iron plays an important role in body's physiology because of its unique ability to give up or accept electrons and oxygen. This enables a rapid change from the ferrous (reduced) to the ferric state (oxidized form) with no expenditure of energy. It has thus a central role in respiration both in the take-up of oxygen in the lungs and its utilization at the cellular level. A large number of foods contain iron (See table 9.2). The concentration varies in accordance with soil conditions so that a range occurs in most vegetable foods. All food iron is present in two main forms:

(1) **Inorganic or non-haem iron**, which occurs as ferric hydroxide complexes loosely bound with proteins, amino acids or organic acids. Prior to absorption, this form of iron must be split from its combination with organic molecules and reduced to the ferrous state. It must be then converted to soluble complexes (chelates) by combining with amino acids polypeptides or sugars. This happens during acid-pepsin digestion in the stomach. Hydrochloric acid in the stomach as well as organic acids in food are both important for this purpose. Reducing substances like vitamin C help in the conversion of ferric iron to the reduced (ferrous) state. In this form iron is more soluble and more readily absorbed. On the other hand, presence of phytates can result in the formation of insoluble salts and prevent absorption. For this reason cereals are a poor source, in spite of their rich iron content. Egg yolk also suffers from a similar disadvantage because of its phosphate content.

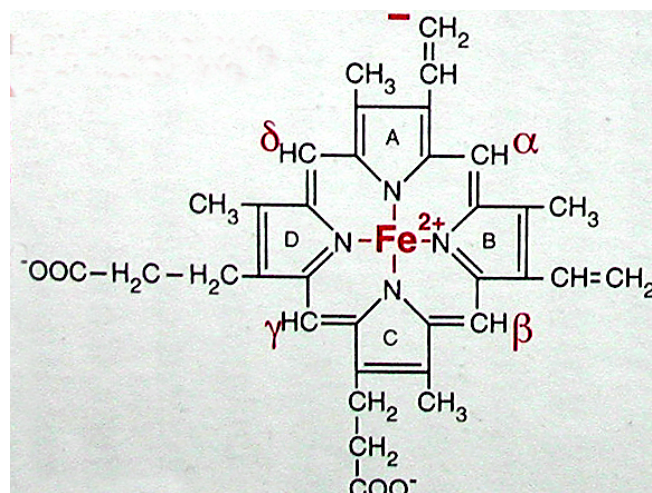
**Table 9.2 Iron content of common foods (recommended intake 10 mg/day)**

Food	Range (mg/1 00 g)
Liver, raw	6.0-14.0
Beef, mutton, raw	2.0- 4.3
Chicken	0.8
Fish (raw)	0.5- 1.0
Eggs (whole, fresh)	2.0- 3.0
Pulses	1.9-14.0
Milletts (raw)	4.0- 5.4
Cereals	9.0 mg
Wheat flour (high extraction)	3.0- 7.0
Wheat flour (low extraction)	0.7- 1.5
Green vegetables	0.4-18.0
Potatoes and root vegetables	0.3- 2.0
Milk	0.1-0.4
Soya flour	12.0 mg

The main sources of iron in the diet are meat, bread, pulses and vegetables.

Several ingenious studies with radioactive iron biologically incorporated into foods have helped our understanding of the absorptive mechanisms and of the availability of iron from various foods. Thus, iron is better absorbed from veal and fish as compared to wheat. The least absorption is from beans, spinach and maize. In general, iron absorption from meals based predominantly on plant foods is quite low (1-5 per cent) and absorption from diets containing adequate amounts of animal protein is higher (8-10 per cent). A diet providing 10-12 mg of iron per day, and in which at least 40 per cent of the iron comes from meat, will provide adequate amounts for normal adults. The average diet in Britain in 1976 provided 12 mg of iron daily. Of this 15 per cent was obtained from white bread and another 23 per cent came from pastries and cereal products. Meat provided about a quarter of the total iron intake, so that more than half the iron intake came from bread, wheat flour and meat. In the average diet haem iron contributes only 1-3 mg of iron per day and in the poorer peasant communities even less. Non-haem iron which forms the bulk of the dietary iron is far less available.

(2) **Haem iron**, (See Fig.9.1) which is bound to porphyrin in haemoglobin and myoglobin. Its absorption is not affected by phytate or phosphate or ascorbic acid. Haem iron is absorbed intact into the intestinal epithelial cells and the iron is split off from the haem moiety within the epithelial cell.



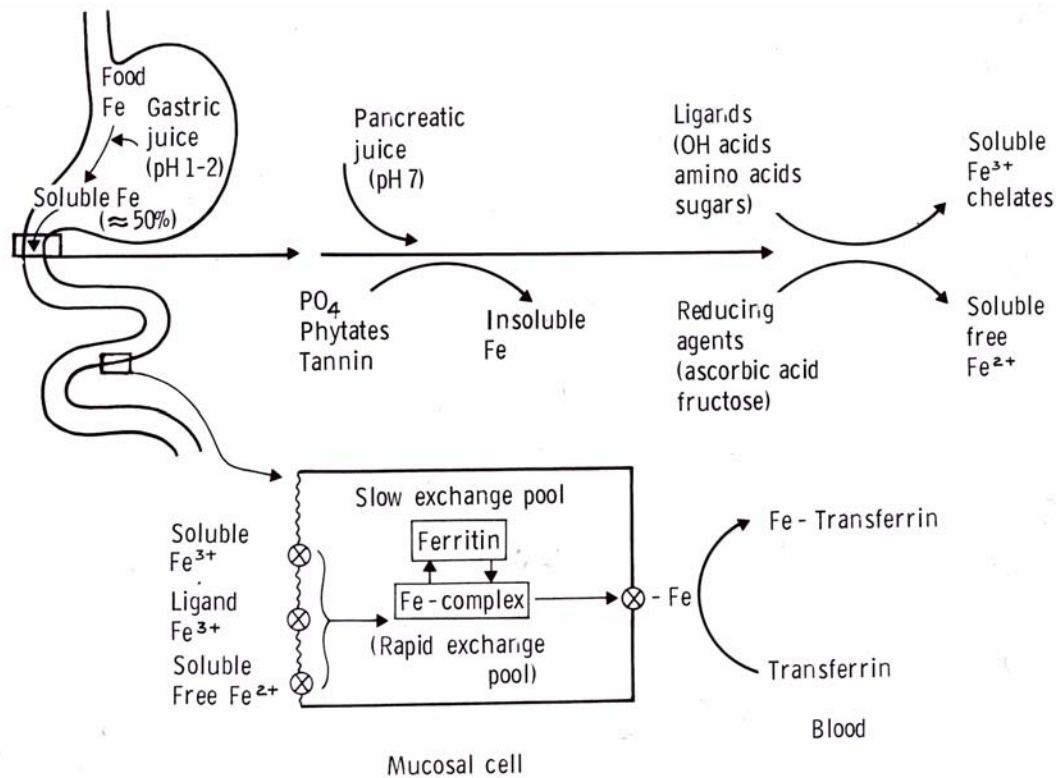
**Figure 9.1 Haem molecule**

Factors influencing absorption of iron are largely those contained in foodstuffs. Inhibitors as well as promoters of iron absorption are present in most foods. Inhibitors like phytates, phosphates and tannins are more common in foods of vegetable origin. The role of tannin has been described only recently. It has been shown that tannin in tea forms insoluble tannate complexes with non-haem iron which cannot be absorbed. The seed coats of legumes, condiments and spices contain appreciable amounts of tannin. On the other hand, ascorbic acid and animal protein, especially meat, help the absorption of iron.

A large proportion of iron is absorbed in the duodenum and the efficiency of absorption decreases from the proximal to the distal parts of the duodenum. Absorption can also occur in the jejunum and proximal ileum. Colonic absorption of soluble ferrous iron has been demonstrated but it is doubtful whether the colon is a significant site of absorption. All ferric iron in the food must be converted to the soluble ferrous form before it can be absorbed. This process commences in the stomach and continues in the small intestine. In people with achlorhydria and in patients after gastrectomy, iron

absorption is decreased. For example, achlorhydria decreases iron absorption by up to 50 per cent. Such individuals cannot increase absorption when iron deficient, and must be given parenteral iron.

Iron taken up by the brush border of the enterocyte rapidly passes into the cell. The quantity of iron transferred from the lumen into the enterocytes depends upon the availability of receptors on the brush border. The receptors compete for iron with the ligand in the gut lumen. Some ligands bind to iron and keep it in solution, thereby promoting its absorption, and others inhibit absorption by precipitating iron. Unlike inorganic iron, haem is not bound to ligands. It can enter the enterocyte directly where the haem molecule is broken down and iron released (figure 9.2).



**Figure 9.2 Physiology of iron absorption**

Within the enterocyte iron is bound to specific carriers and transferred to the serosal side. Here it is delivered to plasma transferrin. Excess iron in the cell which is not transferred to plasma transferrin is taken up by apoferritin and stored as ferritin. Ferritin iron constitutes a slowly exchangeable pool with a half-life of about 4 days. It can be mobilized by combining with carriers. On the other hand it can be lost by the desquamation of cells. Formerly it was believed that iron absorption was determined by the amount of ferritin deposited in the mucosal cell. This "mucosal block" theory is now being discarded. The presently accepted view is that ferritin deals with excess intracellular iron not transferred to plasma.

The gut mucosa plays a regulatory role in iron absorption which depends upon the saturation of the mucosal cells with iron. Several homeostatic mechanisms have been identified as influencing iron absorption. Thus, the state of repletion of body stores, degree of erythropoiesis and hypoxia influence iron absorption but the exact mechanisms regulating absorption are not yet fully understood.

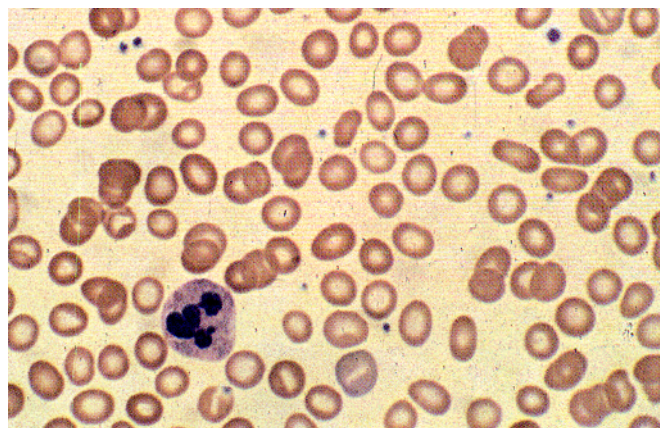
In adults with iron deficiency, 20 per cent of labelled iron can be absorbed compared to less than 10 per cent in controls. In the average Western diet providing between 10 and 15 mg of iron per day, only 5--10 per cent is absorbed. Absorption decreases with advancing age, especially after 60, when iron deficiency is common.

Iron absorbed into the blood stream is carried by transferrin which is a specific plasma protein of the  $\beta$ -globulin group. In the adult male, 200 mg of iron is liberated daily from catabolized erythrocytes and is recycled by the transport system to the bone marrow for incorporation into new red blood cells. The daily turnover of plasma iron is about 35 mg; only a small portion of it is derived from the diet even when absorption has been at a maximum. The total amount of functioning tissue iron in the adult is 300 mg and a significant amount is replaced daily to make good the losses that occur in normal wear and tear. About 1 mg of iron a day is lost from the body in urine, faeces, sweat, and cells shed from the skin and the gastrointestinal tract. Menstrual losses amount to about 20 mg a month. Increased requirements of pregnancy (500 – 1000 mg) contribute to the higher incidence of iron deficiency in women of reproductive age.

**Table 9.3 Daily dietary requirement of iron**

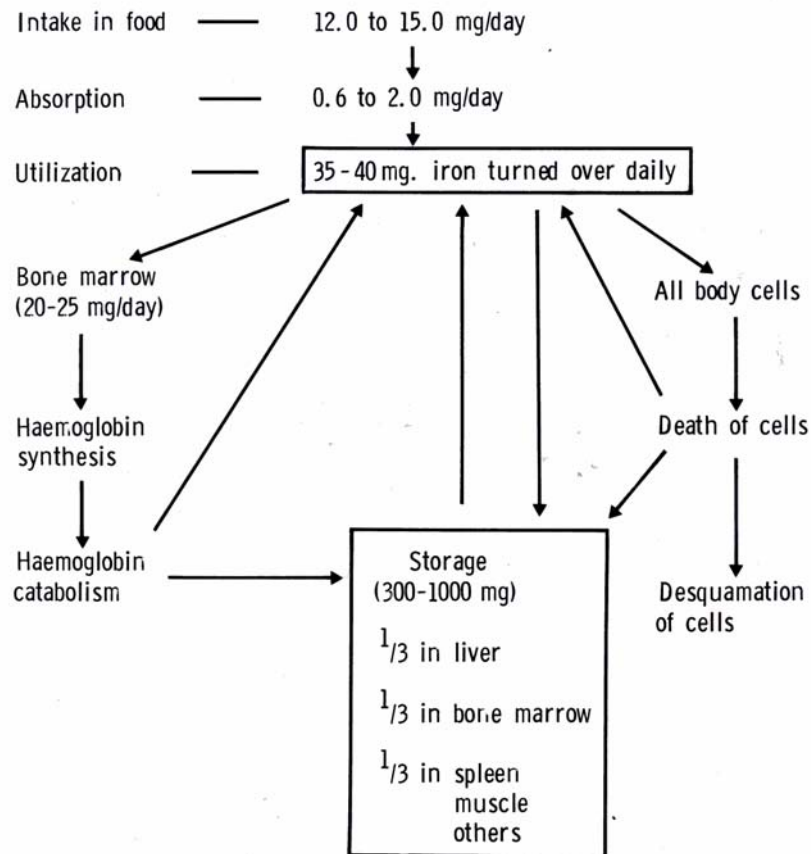
Male	1 mg
Adolescents	2-3 mg
Female (15 to 45 years)	2-3 mg
Pregnancy	3-4 mg
Infancy	1 mg
Maximum bioavailability from normal diet	4 mg

Once the body store of iron is depleted whether due to poor intake or loss from the body a characteristic form of anemia develops in which the erythrocytes are hypochromic, small (microcytes) and irregular in shape (poikilocytes) when seen on a peripheral blood smear. The anaemia is referred to as hypochromic microcytic anaemia with poikilocytes. (See Fig. 9.3)



**Figure 9.3 Hypochromic microcytic anaemia with poikilocytes.**

Iron is stored in the body in the form of ferritin and haemosiderin. Both forms are available to replace lost iron but ferritin is more readily available than haemosiderin. This latter form of stored iron is nearly fixed and takes many years to disappear. Body stores of iron are distributed as approximately a third in the liver, a third in the marrow and another third between spleen, muscle and other tissues (See figure 9.4).



**Figure 9.4 Distribution of iron in the body**

The total amount of iron in the body is between 3 and 5 g, almost two-thirds of it in circulating red cells and 3-5 per cent as myoglobin and in iron-containing enzymes. In all these forms it occurs as haem iron. The remaining 30 per cent is present as non-haem iron, bound to protein for the purpose of storage and transport.

During pregnancy the placenta is a site of significant iron transfer, especially in the later stages. No significant amount of transferrin crosses the placenta so presumably iron is removed from transferrin and taken up by placental receptors, from whence it is then transferred to the fetus. The iron requirements of pregnancy are approximately 2.4 mg/ day over the whole 9 months and the total cost of pregnancy is about 1 000 mg (table 9.4).

**Table 9.4 Iron Requirements in Pregnancy (mg)**

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Basal losses	220
Increase in maternal red cell mass	500
Requirements of the fetus	290
In the placenta	<u>25</u>
Total requirements for the whole pregnancy	1,035

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Because of the requirements of pregnancy and losses in menstrual blood, the iron requirements of a woman in the reproductive period of life are at least twice those of a man or of a post-menopausal woman.

### **PERINATAL ASPECTS OF IRON METABOLISM**

Iron plays a crucial role in early development through its role in a large number of proteins involved in critical cellular processes, such as tissue oxygenation and energy metabolism. It has a significant role in neurodevelopment because of iron containing enzymes involved in brain energy metabolism, neuro transmitter synthesis and myelination. The developing brain undergoes rapid structural and functional changes during the perinatal period and requires a regular supply of iron. Failure to meet the iron demands at this critical period or presence of iron excess appears to have long standing and often permanent adverse effects on neurodevelopment.

Term infants whose gestation has been complicated by maternal severe iron deficiency or hypertension severe enough to cause intrauterine growth retardation, and maternal diabetes as well as pre-term infants are at risk of brain iron deficiency.

Major proportion of fetal iron accretion occurs during the third trimester of pregnancy. Active transport of iron takes place across the syncytio-trophoblast layer of the placenta. Once released into the circulation iron is either utilized immediately or stored as foetal ferritin.

At birth, the normal full-sized infant has a high concentration of iron in the liver, almost 10 times that at 1-3 years of age. The total iron content of such an infant is 250 mg (75 mg/kg) of which 150 mg is present in the red cell mass, 50 mg in tissues and 50 mg as storage iron. A large proportion of iron endowment at birth is in the form of haemoglobin iron. During the first 4 months of life the decreasing haemoglobin mass makes iron available for the needs of the growing tissues. If iron stores at birth are normal; iron absorption has to be enough to provide only for the basal losses. There is growing evidence that the iron content of breast milk is adequate for the purpose and that breast feeding has a protective effect against iron deficiency. Delayed clamping of the cord after birth can increase the blood volume of the newborn by as much as 100 ml, most of which would be broken down and augment the body stores of iron. In communities where iron deficiency is common, maternal anaemia and poor body stores can lead to a low haemoglobin concentration in the cord blood, poor fetal stores of iron and even anaemia in early infancy. For example, at the maternity hospital in Dar-es-Salaam, 100 consecutive cord blood samples showed a mean haemoglobin value of 9.5 g/100 ml (range 6.2-13.8 g/100 ml). The mean haemoglobin of the mothers was 6.8 g/100 ml. Clearly, many of these infants cannot be expected to have normal tissue stores of iron and are likely to suffer from anaemia in infancy.

Perinatal iron deficiency occurs when maternal-fetal iron delivery does not meet foetal iron demand. In developed countries where maternal body stores of iron are mostly adequate, it is gestational conditions such as diabetes and hypertension that are the most common causes of perinatal iron deficiency in full term infants. Both these conditions are characterized by chronic intrauterine hypoxia with compensatory erythropoiesis. Each additional gram of haemoglobin that is synthesized requires an additional 3.5 mg of iron. In diabetes placental vascular disease and decreased placental surface area preclude adequate iron delivery to the foetus.

When foetal accretion cannot meet the needs of erythropoiesis prioritization of iron occurs among foetal organs. Once storage iron reaches its lowest level iron normally destined for organs such as the brain and the heart gets diverted to the erythrocyte. In offspring of diabetic mothers liver iron concentration is decreased by 90%, heart iron by 55% and brain iron by 40%. Similar severity of tissue iron deficiency occurs in infants suffering intrauterine growth retardation due to maternal hypertension. Up to 25% of infants of diabetic mothers and intrauterine growth retarded infants may be at significant risk for brain iron deficiency because of complete loss of storage iron.

Decreased iron delivery to the foetus due to maternal iron deficiency is an important cause of perinatal iron deficiency. In developing countries maternal anaemia (Hb < 8.5 g/100ml) due to iron deficiency affects 30 to 50% of pregnancies and is the most common cause of iron deficiency in the foetus. Preterm birth early in the third trimester before the period of significant gestational iron accretion is another important cause of low iron stores and potential early postnatal iron deficiency.

Follow-up studies of pre-term infants show that iron deficiency can occur within two months of birth. The major cause is the lack of foetal accretion of iron during the last trimester. Low foetal iron stores are further compromised by repeated blood sampling and inadequate iron supplementation.

The iron content of pre-term breast milk is approximately 0.5 mg/litre. Although absorption of iron from human milk is better than from infant formula, iron delivery with exclusive human milk feeding provides only 0.07 mg/kg per day (assuming breast milk consumption of 150 ml/kg per day and 100% absorption). Without supplementation more than 85% of preterm infants on exclusive breast feeding may become iron deficient by 6 months of life. The current recommendation is to begin supplementation at a dose of 2-4 mg/kg per day from the age of 2 months. Even then 15% of preterm infants may have evidence of iron deficiency during infancy.

Iron needs increase significantly with the commencement of erythropoiesis. In full term infants iron stores meet the demands of erythropoiesis for up to four months postnatally. The lower stores of preterm infants are inadequate to sustain erythropoiesis that long. The more rapid rate of postnatal growth with its attendant increase in blood volume places further stress on iron stores. To achieve haematopoietic status comparable to full term infants, preterm infants must increase their total body iron content by approximately 3 to 6 fold during infancy. Without supplementation preterm infants are able to sustain effective erythropoiesis approximately until the doubling of their body weight, which is typically around two months of age. Over 65% of pre-term infants may be iron deficient (serum ferritin < 10 µg/litre) between 3 and 6 months. Extremely low birth weight infants may be already in negative iron balance during the first month.

In the first 2 years of life there is rapid growth, so that birth weight doubles by the age of 6 months, trebles by the age of 1 year and quadruples by the age of 2 years. There is a parallel increase in blood volume and muscle mass and the demand for iron is high in this age group. The requirement during the first year of life is for 200 mg decreasing to 100 mg by the third year. It continues at that level until the ninth year when the requirement increases concomitant with the growth spurt of puberty. Thus, the body needs of iron are high at two periods of life, infancy and pregnancy. In both, the requirements are several times those of the adult male.

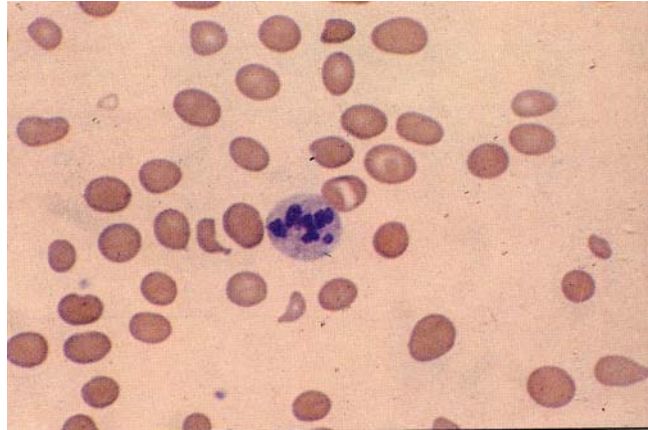
The effects of iron deficiency are pervasive and involve multiple organ systems. Between and within the body organs prioritization of available iron takes place. When hypochromic anaemia is clinically diagnosed it is a late sign and suggests depletion of iron stores. Research in several countries suggests an association between iron deficiency anaemia and abnormal cognitive development in infants <24 months of age. The cognitive deficits appear to correlate with severity of anaemia, are of a long standing nature and do not appear to be correctable with iron rehabilitation. Deficits of reading, writing and arithmetic, spatial memory and attention appear to be particularly associated with iron deficiency in infancy. In older children lower language ability and fine motor skills have been reported in those born with low levels of cord ferritin levels compared to those with normal cord ferritin. In preschool age and older children the developmental adverse consequences of iron deficiency are usually reversible with iron therapy unlike the situation regarding infants. Perinatal iron deficiency is postulated to affect neurodevelopment through its role in neuronal proliferation, myelination, alteration in dopamine and energy metabolism and neurotransmission.

### **Folic acid and vitamin B<sub>12</sub>**

Both these vitamins are necessary in purine metabolism and for the synthesis of DNA. Deficiency causes a characteristic change in nuclear morphology, and the tissues with the highest rate of cell multiplication are affected first. Deficiency is accentuated by any condition causing increased rate of cell multiplication. Thus it is commonly associated with pregnancy, infancy, lactation and adolescence. For the same reason, haemolysis and certain parasitic infections make marginal deficiency more acute by increasing the requirements.

The commonest form in which deficiency presents itself is megaloblastic anaemia. Severe megaloblastic anaemia is infrequent in affluent societies and occurs usually as a complication of a co-existing main disease. No accurate figures are available of the prevalence of megaloblastic anaemia in the tropics, and it is possible that the frequency and. Deficiency can go undiagnosed because it occurs without anaemia or is masked by another haematological or medical disorder.

Megaloblastic anaemia due to deficiency of folic acid is most common in pregnancy. In developed countries the incidence of megaloblastic anaemia in pregnant women attending antenatal clinics is between 2.5 and 5 per cent. The incidence of megaloblastic change in the bone marrow and of low serum folate levels is 8-10 times higher. (See Fig. 9.5). The information is very scanty with regard to developing countries and present evidence suggests that the incidence of megaloblastic anaemia in pregnancy may be between 20 and 50 per cent.



**Figure 9.5 Macrocytic anaemia due to folate deficiency**

In children megaloblastic anaemia is rare in well-nourished communities, except as part of the malabsorption syndrome. In developing countries, megaloblastic anaemia is known to occur in protein-energy malnutrition, especially in pastoral communities living on goat's milk, which is low in folic acid. With cow's milk, boiling or pasteurization can result in the loss of 75 per cent of the folate.

Folate deficiency is a commoner cause of megaloblastic anaemia than deficiency of B<sub>12</sub>, because body stores of folate are more easily depleted than those of B<sub>12</sub> and even a minor degree of dietary lack or malabsorption can precipitate deficiency. Alcohol and several drugs, including anti-malarials, can interfere with folic acid metabolism and cause a deficiency.

In most foods, folic acid (pteroylglutamic acid) occurs in the form of polyglutamates. But only pteroylmonoglutamic acid can be utilized, hence hydrolysis of the polyglutamates of the food is necessary. This occurs in the mucosal cells of the small intestine. Many of the naturally occurring folates are labile and easily destroyed by prolonged cooking. In the average British diet 16-24 per cent of free folate is derived from cow's milk. Liver is a rich source so that even one meal of liver can make a significant contribution to the week's intake. The relative availability of the polyglutamate forms of folic acid and pteroylmonoglutamic acid is not yet clear. On present evidence it would appear that the polyglutamate forms are not as available to the body as pteroyl mono-glutamic acid. Approximately half the folate present in food is retained and the remainder excreted regardless of whether it is ingested as mono or polyglutamate.

Daily requirement of folate is 100-200 µg. (See table 9.5). A normal mixed diet contains about 200 – 300 µg. natural folates, as we have seen, are largely in the polyglutamate form, and these are absorbed through the upper small intestine after deconjugation and conversion to the monoglutamate, 5-methyl tetra hydrofolate. Body stores are sufficient for only about four months. Folate deficiency may arise because of inadequate dietary intake, and malabsorption especially due to gluten induced enteropathy. Deficiency in pregnancy may be due partly to inadequate diet, partly to transfer of folate to the foetus, and partly to increased folate degradation. Active transfer of folate to the foetus takes place in the last weeks of pregnancy. Prematurity has an adverse effect on the amount of folate stored by the foetus. Red cell folate is significantly lower in pre-term infants of 25-37 weeks' gestation (270 ng/ml) as compared to full term infants (340 ng/ml).

Amongst the poorer communities of the developing world, fresh vegetables are the main source of folic acid. However, the increasing cost of fresh vegetables coupled with their relative scarcity in certain seasons may limit intake of the vitamin. Lentils are another good source but they require prolonged cooking. Unless soaked overnight, and preferably sprouted prior to cooking, the prolonged cooking is likely to destroy the folic acid.

**Table 9.5 Dietary requirement for folate**

Group	Safe level of intake ( $\mu\text{g}/24\text{h}$ )
Adult males	200
Adult females	170
Pregnancy	370-470
Lactation	270
Children 1-6 years	50
7-12 years	102
13-16 years	170

The provision of once daily iron and folate supplements throughout pregnancy has been described as one of the most successful preventive interventions. In countries where such prophylaxis is practiced megaloblastic anaemia is now a rarity.

There has been an on-going debate about iron supplementation for children because of possible increase in susceptibility to infection. A recent meta-analysis of several randomized controlled trials involving 7892 children from different regions of the world showed that the overall rate of infection among the iron intervention group was no higher than that in controls. With regard to individual infections there was a small but significant ( $P < 0.04$ ) risk of diarrhoea, which in practice represented only an extra 0.05 diarrhoeal episodes per child per child per year. The meta-analysis supported the safety of iron intervention to anaemic children.

**Vitamin B<sub>12</sub>** exists in nature only as a product of synthesis by microorganisms. Fruit, vegetables, cereals and cereal products are devoid of B<sub>12</sub> and the usual dietary sources are meat and meat products and, to a lesser extent, milk. (See table 9.6). Because of its predominantly animal source, strict vegetarians invariably develop B<sub>12</sub> deficiency over a period of many years, unless they take special measures to avoid it.

In some species such as, for example, the ruminants, vitamin B<sub>12</sub> is exclusively synthesized by the bacteria in the gut. In the human this source is inadequate to meet the requirements of the body, and the vitamin must be supplied in the food. Vitamin B<sub>12</sub> occurs in nature as linked to protein by means of peptide bonds, and is liberated during cooking and digestion.

The body's requirement for vitamin B<sub>12</sub> is about 1  $\mu\text{g}$  daily. This is amply supplied by a normal Western diet (10-30  $\mu\text{g}$  daily). Absorption is limited to 2-3  $\mu\text{g}$  daily. The commonest form of B<sub>12</sub> deficiency is seen in pernicious anaemia. The underlying mechanism is an autoimmune gastritis that results in achlorhydria and the absence of intrinsic factor.

For absorption vitamin B<sub>12</sub> must first combine with the intrinsic factor secreted by the cells of the gastric mucosa. The vitamin B<sub>12</sub> intrinsic factor complex then attaches itself to receptor sites on the mucosal cells of the ileum where vitamin B<sub>12</sub> is absorbed. The average diet in Britain provides approximately 5  $\mu\text{g}/\text{day}$  of vitamin B<sub>12</sub>. Little is known about average intakes in developing

countries and one estimate puts it as between 0.5 and 2.0 ug. The maximum amount of the vitamin that can be absorbed at any given meal is between 1.5 and 3.5. ug. The intake from three well-balanced meals in one day will thus provide enough vitamin B<sub>12</sub> to meet the daily requirement of 2-5 ug. Even the grossly inadequate diet consumed by some old people contains enough vitamin B<sub>12</sub> to prevent anaemia and therefore a nutritional cause for a deficiency is rare.

**Table 9.6 Daily requirement of vitamin B<sub>12</sub>**

<b>Group</b>	<b>Safe level of intake (ug/24 h)</b>
Adults	1.0
Pregnancy	1.4
Lactation	1.3
Infants	0.1
Children 1-10 years	0.04 ug/kg
Children 11-16	1.0

Studies of erythropoiesis in megaloblastic anaemia indicate that in this state ineffective erythropoiesis may represent as much as 63 per cent of total erythroid activity. The bone marrow is capable of sustaining erythropoiesis at up to seven times the normal rate, but the proliferative effort only results in an increased number of abnormal cells, which may be destroyed within the marrow or, if delivered into the circulation, are short-lived. The net result is that cell destruction is far greater than erythropoiesis, with consequent anaemia.

Pregnancy and lactation increase the requirements of both folate and vitamin B<sub>12</sub> in the same way as they do for iron. Hence megaloblastic anaemia more commonly occurs in pregnancy, especially in communities where marginal deficiencies occur. In one study of 1000 pregnant women in South India almost a third had a haemoglobin concentration of less than 10 g/100 ml. Evidence of macrocytosis in the blood smear was found in 27 per cent, but the bone marrow showed a megaloblastic picture in 60 per cent. The mean concentration of serum folate was significantly lower than in female controls. Many of the pregnant subjects showed clinical signs of nutritional deficiency like glossitis (19 per cent), stomatitis (7 per cent) and koilonychia (8 per cent). Serum folate levels were particularly low in such cases, indicating that several deficiencies co-existed. It is important that body stores of nutrients are made up after a pregnancy because if the diet is inadequate and a deficiency continues until the next pregnancy, the baby will be born with poor body stores. As we have seen, such a continuing deficiency occurs with regard to iron, resulting in low haemoglobin values of cord blood, poor fetal stores of iron, and anaemia in infancy. Recovery of body stores of iron, folic acid and other nutrients may occur during school age, but body requirements increase again to sustain the growth spurt at adolescence. In many peasant communities early marriage and child-bearing is the rule, so that if a deficiency persists at adolescence it is transmitted to the offspring. Thus, in poor communities nutritional anaemia, especially anaemia due to iron deficiency, tends to be carried forward from one generation to another.

Folic acid deficiency also occurs in pre-term infants. Demands of growth exceed intake of the vitamin and they use up their tissue stores which, in any case, may be less than normal.

At birth serum and red cell folate levels are high in both pre- and full-term infants compared with adult values. In the cord blood the concentration of folic acid is about three times that in the maternal blood, indicating active transfer of folic acid from the maternal to the fetal side of the

placenta. Similarly there is preferential transfer of vitamin B<sub>12</sub> to the fetus. It is estimated that 0.2 ug/day of vitamin B<sub>12</sub> is transferred from the mother to the fetus during the latter half of pregnancy. Folate levels drop rapidly soon after birth in all infants, but the drop in value is more rapid and more severe in pre-term infants. The newborn infant's requirement for folate in milk feeds is 20-50ug/1, and most proprietary milk formulae also provide the same amount. Warming the feeds after reconstitution for the purpose of sterilizing will destroy the folate. For example, it has been shown that boiling for as little as 5 seconds reduces the folate content by 50 per cent. Folate deficiency should be suspected in all anaemic pre-term babies and particularly in those with very low birth weights or those with a history of feeding difficulties.

In infants, repeated infections are known to cause anaemia with megaloblastic changes in the bone marrow. Similarly haemolysis due to any cause, e.g. malaria or sickle cell anaemia, increases the requirements of folic acid to meet the needs of a hyperactive marrow.

Megaloblastic anaemia due to deficiency of vitamin B<sub>12</sub> is comparatively rare and is usually restricted to undernourished communities who are on a predominantly vegan diet, for religious or cultural reasons. A megaloblastic anaemia caused by the fish tapeworm *Diphyllobothrium latum* is found in Scandinavia, Japan and the Great Lakes region of the United States and Canada and is due to a deficiency in the host caused by the tapeworm which diverts the vitamin in the gut lumen for its own use. In heavily infested areas of Finland up to 27 per cent of the population are known to be carriers, and one in 50 such carriers is known to develop megaloblastic anaemia.

### **Vitamin B<sub>12</sub> neuropathy.**

A minority of patients with vitamin B<sub>12</sub> deficiency develop a neuropathy due to symmetrical damage to the peripheral nerves, and posterior and lateral columns of the spinal cord. The legs are usually more affected than the arms. Psychiatric abnormalities and visual disturbances may also occur.

### **Loss of nutrients**

There are no physiological mechanisms for the excretion of iron except through the desquamation of cells lining the gut and of the skin. Hence the amount of iron in the body is mainly controlled by absorption.

The main cause of loss of iron from the body is through chronic blood loss - either from heavy menstrual periods or from the gut. In the tropics hookworm and *Trichuris* infestations are well-known causes of iron deficiency anaemia. The adult worm is firmly attached to the mucosa of the gut and obtains blood from the host for its own needs of oxygen and glucose. Experiments with labelled iron in volunteers indicate that in heavy infections considerable quantities of blood may be lost (table 9.7). In such cases the losses cannot be recovered from the daily diet and over a period of time a debilitating chronic anaemia develops. As a general rule, above a critical load of 2000 eggs of hookworm per g of faeces severe iron deficiency and anaemia are likely to occur.

**Table 9.7 Faecal blood losses due to intestinal parasites (ml/day)**

	<b>Per parasite</b>	<b>Per 100 eggs in 1g of faeces</b>
<i>Necator americanus</i>	0.02-0.07	2.1
<i>Ancylostoma duodenale</i>	0.14-0.26	4.4
<i>Trichuris trichuria</i>	0.005	0.25

Several cultural practices in traditional societies can contribute to iron deficiency through bleeding at periods when the body needs of iron are greatest. In several traditional societies of tropical Africa the cutting of the uvula as a treatment for cough or for its prophylaxis is a common practice. In many instances the procedure is carried out when the infant is 3 days old and in some communities up to 96.2 per cent of infants have undergone the procedure before the age of 6 months. Similarly female circumcision is widely practiced in tropical Africa. Blood loss at the time of the operation, and the recurrent oozing of blood from the site, may contribute to iron deficiency, especially if body stores are poor or during periods of rapid growth.

Where malaria is endemic it is a major cause of anaemia. Haemolytic anaemia is a common complication of pregnancy in Nigeria and responds to treatment with anti-malarial drugs and folic acid. It has been postulated that haemolysis in malaria is always in excess of the destruction of erythrocytes by the malarial parasites. This is because of an immunological response to malaria by the host. The body stores of iron, folic acid and other nutrients soon get exhausted because of an overactive marrow and because the poor diet supplies very little.

In addition to the direct effect on the erythrocytes, repeated malarial infection is also responsible for a chronic anaemia associated with enlarged spleen. In the so-called tropical splenomegaly syndrome, parasitaemia is scanty or absent and the red cell morphology resembles that of iron deficiency. Studies with labelled iron have shown a high plasma turnover of iron. A large number of erythrocytes are trapped in the enlarged spleen and represent a considerable portion of the red cell mass, which may be between 50 and 75 per cent of the total pool. It is likely that sequestration of such a large number of erythrocytes results in active erythropoiesis by the marrow, using up the available stores of iron and folic acid.

Folic acid deficiency at times associated with a deficiency of vitamin B12 is common in tropical sprue. Here morphological changes in the mucosa due to the enteropathy combine with excessive bacterial growth with folic acid and vitamin B12 is rapid. Those patients who do not respond to treatment with the vitamins alone may require the addition of antibiotics.

In conclusion, nutritional anaemias are the second largest group of nutritional disorders after protein-energy malnutrition. The individual is most vulnerable at those periods of life when the requirements for nutrients are increased because of the demands of growth. In many parts of the tropics nutritional anaemia is particularly common on account of inadequate nutrition and super-added parasitic or helminthic infections which further increase the requirements of nutrients. In many of the affluent societies of Western Europe, nutritional anaemia used to be a public health problem not so very long ago. The present improvement has been brought about by better standards of health care, especially during infancy and pregnancy, and better nutrition, together with public health measures.

### FURTHER READING

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