

## Review

### IRON DEFICIENCY IN CHILDREN: DETECTION AND PREVENTION

Despite a plethora of papers, reports and consensus statements during the last 25 years concerning the high prevalence and complications of iron deficiency (ID), the problem is still with us. A recent national study in Britain showed that 12% of 2-year-olds were anaemic, rising to 29% in Asian immigrant groups (Lawson *et al.*, 1998). What can be done about it? This paper reviews detection and prevention of iron deficiency anaemia (IDA) referring mainly to studies published in the last 5 years.

Earlier substantial reviews of iron nutrition are available (Brock *et al.*, 1994; British Nutrition Foundation, 1995; Hallberg & Asp, 1996). Reviews specifically related to children include those by Oski (1993) and Wharton (1999a).

#### DETECTION

Detection is divided into indications for investigation, which investigations to apply, and their interpretation.

##### *Indications for investigation*

*Clinical presentation.* There are obvious indications for determining iron status in some clinical presentations. An example is suspected malabsorption. One study found that an oral iron absorption test was more sensitive as a screening test for upper intestinal absorption than the commonly used D-xylose method (Stahlberg *et al.*, 1991; de Vizia *et al.*, 1992). Other deficiencies often coexist with ID partly because a poor diet may have many deficiencies but also because of micronutrient interaction, e.g. ID with deficiencies of vitamin A or D (Gujral & Gopaladas, 1995; Underwood & Arthur, 1996; Wharton, 1999b). ID may play a role in or complicate such diverse disorders as ischaemic stroke, apparent asthma, cyanotic heart disease and gastric trichobezoar (Hartfield *et al.*, 1997; Hetzel & Losek, 1998; Olcay *et al.*, 1996; Phillips *et al.*, 1998).

In my view any child reaching hospital as an outpatient or inpatient should have their haemoglobin level and RBC indices determined. Some specialities argue this is unnecessary since the haemoglobin distribution in their patients is no different to that in the general population (e.g. in otolaryngology; Heaton *et al.*, 1991). This seems a lost occasion for opportunistic screening for a common disorder. Clinical signs are helpful only in severe anaemia, but surveys show that pale conjunctivae (sensitivity 74%) and nail beds

(specificity 96%) are useful signs (Thaver & Baig, 1994). Blue sclerae might be an extra sign (Beghetti *et al.*, 1993).

*Age of the child.* The highest prevalence of iron deficiency anaemia (IDA) occurs in toddlers and adolescents because the increment in haemoglobin iron per unit body weight is greatest at these ages (see Fig 1).

Two points should be noted. There is little increase in total body iron in the first 4 months or so of life. As the haemoglobin falls from around 18 g/dl at birth to 14 g/dl during the first 2 weeks of life the liberated iron is stored and then gradually reused as the total mass of circulating haemoglobin begins to increase with growth. Between 4 and 12 months total body iron increases by about 130 mg, and an external source of iron is necessary. If not met, ID occurs and frank anaemia develops usually after the first birthday. Note also that boys need more iron at adolescence because of the increase of muscle and myoglobin. Subsequently these increased requirements due to changes in body composition subside, but increased requirements continue in girls following menarche.

*Dietary history.* Infants who continue to receive only breast milk after the first 6 months of life are at increased risk. Breast feeding may continue after 6 months without difficulty so long as other foods providing available iron are introduced.

Also at risk are infants who, despite current policy, are changed from an infant formula to whole cows' milk before the age of 1 year. It is not clear whether the higher prevalence of IDA in these infants is mainly the effect of an inadequate intake of dietary iron or due in addition to increased intestinal iron loss (Ziegler *et al.*, 1990; Fuchs *et al.*, 1993a, b).

In toddlers attending well child facilities in Cleveland, U.S.A., a simple dietary history predicted microcytic anaemia (sensitivity 71%, specificity 79%), but a quarter of the anaemic children were not identified (Boultry & Needlman, 1996). A community study in Sydney found a low consumption of meat (i.e. haem iron) and introduction of whole cows' milk before the first birthday were significant indicators of ID (Mira *et al.*, 1996).

Many adolescent girls try to control their weight and inadvertently limit iron intake. This was particularly marked 10 years ago in British girls who bought snacks from local shops rather than eating school lunch or food from home, but there has been evidence of improvement since then (Department of Health, 1989; Moynihan *et al.*, 1994; Southon *et al.*, 1994; Doyle *et al.*, 1994). Many adolescents pass through a temporary period of vegetarianism because of concerns with animal welfare. Although adequate iron nutrition is achievable on a vegetarian diet it must provide

Correspondence: Dr B. A. Wharton, MRC Childhood Nutrition Research Unit, Institute of Child Health, Guilford Street, London WC1N 1EH.

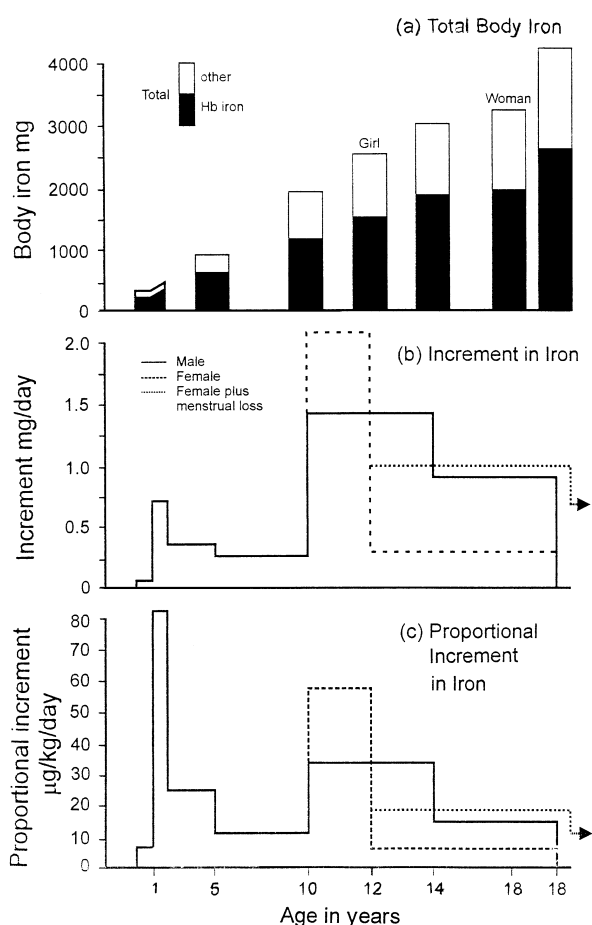


Fig 1. Changes in body iron during development: (a) total body iron and haemoglobin iron (mg) in males except where shown; (b) daily increment in body iron (mg/d): —, male; ---, female; ···, female plus menstrual loss; (c) proportional daily increment in body iron ( $\mu\text{g}/\text{kg}/\text{d}$ ): symbols as for (b).

iron sources (such as pulses) and enhancers of absorption (e.g. vitamin C and fish or poultry if acceptable), and the temporary amateur vegetarianism may not ensure sufficient absorbed iron.

**Other factors.** Preterm babies are born with a lower concentration of haemoglobin, so any physiological haemolysis liberates less iron for stores; erythropoietin, if given, increases iron requirements, and so does catch up growth. Light for gestational age babies often have a raised haemoglobin at birth reflecting intrauterine hypoxia, and so initially, post haemolysis iron stores are higher but the rapid catch-up growth increases demands. In a normal term baby the total haemoglobin mass doubles during the first year of life (from 180 mg at birth to 340 mg at 1 year). In a preterm 1 kg baby the increase is 6-fold (50–300 mg). In a 2 kg baby born at term the increase is 3-fold (110–330 mg).

Children of immigrants or refugees have a higher prevalence of iron deficiency, presumably due to such factors as socio-economic deprivation (living in inner city areas with overcrowding and limited parental income), language

difficulties (health education is difficult), unfamiliarity with foods available in the new environment (often a tendency to rely on milk and puddings), food customs which are difficult to follow (e.g. halal meat for Muslims may not be easily available and so children are given a meat-free diet by a mother inexperienced in providing a balanced vegetarian diet). In a nationally representative survey of British 1.5–2.5-year-olds 12% had IDA but among children of immigrant families it was higher: India (20%), Pakistan (27%) and Bangladesh (29%) (Lawson *et al*, 1998). Other recent reports describe the problem in children from South-East Asia, Latin America and Eastern Europe living in U.S.A., Norway and Switzerland (Graham *et al*, 1997; Sargent *et al*, 1996).

Athletic performance, particularly endurance sport, may lead to blood loss from the gut and urinary tract (Robertsson *et al*, 1987; Haymes & Lamanca, 1989). Therefore athletic girls who have passed menarche and are trying to slim may be at particular risk of iron deficiency.

#### Which investigations

The staging of iron status by Osaki *et al* (1983) is a useful concept and various measurements can be used to define the stages.

**Iron sufficiency.** Iron stores and erythropoiesis normal.

**Iron depleted.** Erythropoiesis normal but iron stores reduced (serum ferritin  $<12 \mu\text{g}/\text{l}$ ) indicating a reduction of iron in the bone marrow, liver and other parts of the reticuloendothelial system (note that the exact cut-off point for normal/abnormal ferritin depends on the method used; a reference ferritin preparation to calibrate the assay is recommended).

**Iron-deficient erythropoiesis.** (i) Abnormal RBC biochemistry (free erythrocyte protoporphyrin (EPP)  $>99 \text{ nmol}/\text{mol}$  haem; serum transferrin receptor raised, e.g.  $>8.5 \text{ mg}/\text{l}$  but exact cut-off depends on age and the assay used); (ii) abnormal RBC morphology (microcytosis,  $\text{MCV} <80 \text{ fl}$ , varying with age; anisocytosis,  $\text{RDW} >15\%$ ); (iii) transport iron reduced (transferrin saturation  $<10\%$ ).

**Iron deficiency anaemia.** The above plus haemoglobin  $<11 \text{ g}/\text{dl}$ .

There is no evidence that iron depletion or iron-deficient erythropoiesis alone have any adverse clinical effects, whereas iron deficiency anaemia is associated with alterations of immunological, gut and mental function.

In the recent NHANES survey in the U.S.A. (Dallman *et al*, 1996) ID was defined as the presence of two or more abnormal measurements as shown in Table I. Although one can argue about the exact cut-off points used and the need for two abnormal characteristics, this battery of tests was applied to a large number of children and the haemoglobin ranges produced (i.e. after excluding children with more than one abnormal test) are suitable reference standards (see Table I). A recent survey in Bristol has suggested a cut-off point for haemoglobin concentration in 12- and 18-month-olds as low as 10 g/dl, but no attempt was made to exclude iron-deficient children and the haemoglobin method used was the Hemocue B-Hb photometer (Sherriff *et al*, 1999).

It would be impractical, however, to use initially the whole

**Table I.** Cut-off values for laboratory tests of iron status, and haemoglobin reference values for non-black children who had fewer than two abnormal tests in NHANES survey in U.S.A. (Dallman *et al.*, 1996).

	Age (years)				
	1-2	3-5	6-11	12-15 M	12-15 F
Cut-off values					
Transferrin saturation (%)	9	13	14	14	14
Serum ferritin ( $\mu\text{g/l}$ )	10	10	12	12	12
Erythrocyte protoporphyrin ( $\mu\text{g/dl RBC}$ )	70	70	70	70	70
MCV (fl)	77	79	80	82	85
Reference haemoglobin values (g/dl)					
Mean	12.0	12.3	13.0	14.1	13.3
(SD)	(0.65)	(0.7)	(0.75)	(1.05)	(0.9)
Mean -2SD	10.7	10.9	11.5	12.0	11.5

battery of investigations shown in Table I and simpler approaches for population and individual studies have been suggested.

*Haemoglobin concentration alone.* Yip *et al* (1996) suggested that haemoglobin concentrations alone could be used in populations. The distributions of haemoglobin are determined in children and adults. If the distribution is moved to the left, in both children and women of child bearing age but not in men, then iron deficiency is likely. If the distribution is moved to the left in men as well, then probably other factors are operating as well, e.g. malaria or hookworm. This approach has been used to diagnose dietary ID in Pakistan, iron losses from hookworm in Zanzibar, and iron losses (from undetermined causes) in Alaskan natives (Petersen *et al.*, 1996). The strategy has been questioned in Thailand for children >5 years of age in whom anaemia was rarely associated with a low plasma ferritin (Linpisarn *et al.*, 1996).

*Haemoglobin and RBC indices.* Electronic counters based on impedance or light scattering are in common use in developed countries. The likelihood of iron deficiency may then be assessed from the indices. Increasing use is now made of histogram distributions of red blood cell volume rather than using only arithmetic summaries of size and variation in size such as mean corpuscular volume (MCV) and red cell distribution width (RDW). With some methods 'red cell cytograms' are also available in which red cell volume is plotted against red cell haemoglobin concentration for all red cells counted. Walters & Abelson (1996) have described the interpretation of full blood count and indices, possible artefacts (due to cold agglutinins, high white cell counts, and hyperosmolar plasma), crude checks for internal consistency (haemoglobin in g/dl about  $3 \times \text{RBC}$ ; calculated and correct PCV about  $3 \times \text{haemoglobin}$ ) and its interpretation in children. Hinchcliffe & Helliwell (1993) have described the use of distribution histograms and cell cytograms in children.

Typically in iron deficiency anaemia Hb and MCV are reduced, RDW is increased (i.e. microcytosis and anisocytosis), red cell haemoglobin distribution width (HDW) is

increased (i.e. anisochromia), and the 'shape' of the cell cytogram scatter is moved down and to the left with a large proportion of cells in the hypochromic microcytic zone. During a response to iron treatment double peaks are seen in the histograms for red cell volume and red cell haemoglobin and the cytogram shows more cells in the normocytic normochromic zone. The application of these more sophisticated methods to population screening has not been evaluated. Mates *et al* (1995) argued that a full electronic counter blood screen is a 'watchdog of community health'. In their Israeli series including adults as well as children, 1% had microcytosis, mostly due to iron deficiency (58%) and thalassaemia minor (35%). Similarly Kim *et al* (1996) recommend that MCV and RDW be routinely determined, and this increases the predictive value for iron deficiency to 98%. Choi & Reid (1998) found RDW a useful predictor of red cell disease in the well baby clinic.

*Other investigations.* EPP alone (or zinc protoporphyrin, ZPP) has been used for screening and as an indication for a therapeutic trial of iron in some American paediatric practices (Benjamin *et al.*, 1991; Siegal & Lagrone, 1994). In iron deficiency zinc fills the iron pocket in the protoporphyrin molecule. ZPP determination requires only 20  $\mu\text{l}$  of blood and is easily measured in a haematofluorimeter. It also remains abnormal for a week or so, even if iron therapy commenced before the test. However, it is also abnormal in the anaemias of inflammation and in lead poisoning.

Serum ferritin may also be determined on small blood samples, but careful standardization of methods and use of a reference ferritin preparation for calibration are necessary (Worwood, 1997). It is raised during acute infections, chronic disease and liver disease irrespective of the iron stores, but iron deficiency is the only cause of a low concentration.

Serum transferrin receptor concentration has raised considerable interest. The concentration reflects the number of transferrin receptors on immature red cells and so in most instances also reflects the rate of bone marrow

erythropoiesis. Iron deficiency, however, also results in an 'unproportional' increase in the concentration (Heubers *et al*, 1990). An increased concentration provides an early and sensitive indicator of functional iron deficiency, sometimes before the plasma ferritin has fallen (Skikne *et al*, 1990; Worwood, 1995, 1997). A major advantage is that it remains normal in many chronic disorders if iron deficiency is not present. However, it is raised in the thalassaemias even though iron deficiency is not present. As in adults, in infants and 11–12-year-old boys higher concentrations of the receptor were associated with a lower serum ferritin even within the normal physiological range for ferritin (Virtanen *et al*, 1999). However, its use as an index of iron deficiency in infancy and adolescence has been questioned (Kuiper-Kramer *et al*, 1998; Kling *et al*, 1998; Kivivuori *et al*, 1993; Kuizon *et al*, 1996). It would be unwise to use the test alone without other measurements of ID as well.

#### Interpretation

Hereditary causes of microcytosis, inflammation and various chronic diseases, and occasionally lead poisoning, may cause difficulties of interpretation.

**Microcytosis.** Apart from the thalassaemias, hereditary causes of microcytosis are quite rare. Most are associated with iron overload of tissues, but a small number of children have been described with ID because of a defect in absorption (Table II).

The RBC in IDA and the thalassaemias have similar indices. The degree of anisocytosis and hence the RDW is usually higher in IDA, particularly in relation to the degree of microcytosis. Various mathematical ratios of red cell indices have been suggested to help the differentiation. Using cytometry plots, the proportion (%) of hypochromic cells is greater than the proportion of microcytic cells in iron deficiency, whereas the reverse is true in thalassaemia (d'Onofrio *et al*, 1992). In thalassaemia there also may be an increase in hypochromic macrocytes. When there is any possibility of a thalassaemia, however, it is usually better to

proceed directly to haemoglobin electrophoresis and A<sub>2</sub> determination, but iron deficiency in association with thalassaemia may temporarily mask the characteristic changes in A<sub>2</sub> and HbF. In a United States study a half of people (aged 15–49 years) with beta thalassaemia trait, had a raised ZPP, and so did a quarter of those with haemoglobin E or alpha-thalassaemia trait, suggesting that ZPP may be abnormal in thalassaemia traits, but the exact iron status of the subjects was not defined (Graham *et al*, 1996).

**Inflammation.** The anaemias of infection and chronic diseases are classically normochromic and normocytic, but hypochromia and microcytosis occur in about a third of infected children. Even after a mild infection many measurements move in the same direction as occurs in ID, but ferritin rises and serum transferrin receptor remains normal (see reviews by Abshire, 1996, and Walter *et al*, 1997). On the other hand, tropical infection such as malaria did not interfere with the use of EPP and ferritin in the diagnosis if ID of Zanzibari schoolchildren (Stoltzfus *et al*, 1997).

In chronic disease such as rheumatoid arthritis interpretation is difficult. Although measurements suggesting ID may be due to cytokine activity true ID (demonstrated by bone marrow examination) may also occur. Moreover, serum transferrin receptor is raised in a number of patients, suggesting iron deficient erythropoiesis which may respond to intravenous iron saccharate (Cazzola *et al*, 1996).

**Lead poisoning.** The anaemia is classically normocytic and normochromic, but ID is often present as well, modifying the RBC morphology. ZPP is raised, not because of insufficient iron to join protoporphyrin to form haem but because ferrochetalase, which catalyses the reaction, is inhibited by lead.

There is variable evidence linking iron deficiency with an increased risk of lead poisoning (Sargent *et al*, 1995; Hammad *et al*, 1996). Some years ago anaemia with pica would prompt investigation for both disorders, but as environmental lead has decreased the diagnosis is less common. If in doubt, the blood lead levels should be

**Table II.** Hereditary causes of microcytic hypochromic anaemia.

With iron overload	
Thalassaemias: autosomal recessive	
Atransferrinaemia: autosomal recessive	Goya <i>et al</i> , 1972
Without iron in marrow: two siblings	Shahidi <i>et al</i> , 1964
With eliptocytosis: sex-linked recessive	Cooley, 1945
Sideroblastic anaemias	
Some are pyridoxine responsive with hypolipidaemia	Spitzer <i>et al</i> , 1996
With delta aminolevulinic acid synthetase deficiency	Aoki <i>et al</i> , 1973
With cytomegalovirus	Goedseels <i>et al</i> , 1997
Without iron overload	
Iron malabsorption*: three siblings	Buchanan & Sheehan, 1981
Iron malabsorption*: partial response to parenteral iron: two siblings	Hartman & Barker, 1996

\*Some similarities to recessively inherited microcytic anaemia of the mk-mk mouse which may be due to a defective transferrin receptor leading to impaired cellular uptake of iron (Bannerman, 1981).

determined and the response to iron noted. Lead diuresis and reduction in blood lead following chelation treatment are less in iron-deficient children (Ruff *et al.*, 1996; Markowitz *et al.*, 1997).

## PREVENTION

### *Screening*

Screening is a form of secondary prevention, detecting and treating the disorder early before serious problems occur. If timed at the age of peak incidence (at 18 months), many children would have been anaemic for some months. If introduced earlier, e.g. 13 months at the time of MMR immunization, a number of children not anaemic then become so some months later. In Bristol a quarter of children found to be anaemic at the age of 2 years had not been so at 13 months (James *et al.*, 1993). An ideal age for screening is therefore not apparent. All children in particular groups might be screened if the prevalence of IDA is high in the group, e.g. in inner city areas, children of immigrant or refugee families, exclusively breast-fed 10-month-olds, and toddlers in whom cows' milk was the main drink before 12 months of age.

### *Overall preventative strategy*

Various bodies have suggested strategies, e.g. government-funded bodies: the Centres for Disease Control (1998) in Atlanta; Department of Health (1994) in U.K.; non-government organizations such as the British and Swedish Nutrition Foundations; many individual nutritionists and paediatricians (Wharton, 1999a; Ziegler & Fomon, 1996).

*At birth.* Blood loss should be avoided. Effective umbilical clamping with devices which tighten as the cord withers usually prevent cord haemorrhage. The time of clamping may affect subsequent ID. In Guatemala infants in whom the cord was not clamped until pulsation had stopped had a higher haematocrit at 2 months of age; this manoeuvre had no effect on serum ferritin at 3 months of age in Indian children (Grajeda *et al.*, 1997; Geethanath *et al.*, 1997). Since three-quarters of iron 'stored' at birth is in haemoglobin, perinatal blood loss is a potent cause of anaemia in early and later infancy. Generally the other stores in newborns show little relationship to the mothers' iron status, although some studies in both the developed and developing world have shown one. Two papers have shown that poorer maternal iron status in pregnancy is associated with a poorer iron status in the infants at 1 year of age (Strauss, 1996; Colomer *et al.*, 1990). This could reflect a longer-term effect of reduced iron stores or that both mother and child have received an iron-deficient diet.

*Suckling period (0–4 months).* For normal-sized babies there is little concern because total body iron does not increase during this time. If ID occurs then abnormal blood loss should be considered. This may occur in the perinatal period (e.g. fetomaternal transfusion, cord accident) or later (e.g. reflux oesophagitis, bleeding from ectopic gastric mucosa in a Meckels diverticulum, rarely allergic colitis of infancy). Breast feeding is encouraged, or failing that a modern infant formula is used.

*Weaning: continuation of the suckling's food.* From the age 6 months a dietary source of iron is necessary. For bottle-fed babies this is easily provided by continued use of an infant formula which is iron fortified or introduction of a follow-on formula, all of which are iron fortified. Breast milk alone will not supply the extra iron but absorption of the small amount of iron present is high.

*Weaning: introduction of weaning foods containing available iron.* This is less critical in bottle-fed babies receiving iron-fortified formula or a follow-on milk, and bottle-fed babies tend to receive weaning foods from an earlier age than breast-fed ones (White *et al.*, 1990). Although there is evidence that too early an introduction of solid foods interferes with iron absorption from breast milk (Pisacane *et al.*, 1995), they should be introduced from 6 months of age. Meat, because of its haem iron, is an excellent choice, providing zinc as well, which may also become a limiting nutrient in prolonged breast feeding. A Danish study showed that an intake of 27 g of meat a day from the age of 8 months (compared to an intake of 10 g daily) led to lower falls of haemoglobin in later infancy, although there were no effects on serum ferritin or transferrin receptor concentrations (Engelmann *et al.*, 1998). Unfortunately many mothers who continue to breast feed their older infants choose vegetarian weaning foods from which iron is less available. Convenience weaning foods are widely available in the Western world, and some are fortified with iron. Wide use of these foods provided a more satisfactory diet (more iron, less protein, salt and sugar) than a home-made diet alone (Mills & Tyler, 1992; Stordy *et al.*, 1995).

Work in Honduras questioned the possibility of giving iron supplements to breast-fed children from about 4 months rather than run the risk of introducing microbe-contaminated feeds which anyway have low iron availability (Dewey *et al.*, 1998).

*Family foods containing available iron.* In Britain 12–15% of the total iron intake of children 1–15 years old is provided by meat, i.e. 4–5% as haem iron, 20–30% by fortified cereal products such as breakfast cereals and bread; vegetables, biscuits and chips (french-fried potatoes) each supply 5–10%. This diet meets the 'reference nutrient intake' (RNI) for most ages but not for toddlers age 1.5–2.5 years (mean intake was 73% of RNI; 100% is desirable), nor for girls aged 10–15 (63% of RNI) (Department of Health, 1989; Gregory *et al.*, 1995). However, the total intake is only part of the story. The absorption of iron is determined by the overall composition of the meal, the integrity of the gastrointestinal tract, and systemic factors. Absorption of haem iron increases when anaemia is present but is little affected by other components of the meal. Absorption of non-haem iron is enhanced by vitamin C, other organic acids present in fruit and vegetables such as citric and malic acid, and animal protein. Absorption is inhibited by phytate, calcium and polyphenols (in tea). For detailed reviews see Lynch (1997) and, specifically for children, Lonnerdal (1990) and Fomon (1993). The extent of iron absorption is also affected by body stores, the rate of erythropoiesis, and hypoxia. The mechanisms whereby enterocytes receive information from these factors to alter absorption are not clear.

In developing countries, fortified foods are less available at affordable prices, and fibre and phytate intakes are higher (Tatala *et al.*, 1998). On the other hand, some foods are cooked in iron pots leading to better iron status than if aluminium pots are used (Borigato & Martinez, 1998). Grape molasses is used as a reasonable source of iron in Turkey (Aslan *et al.*, 1997).

*Avoidance of blood loss.* The role of pasteurized cows' milk in intestinal blood loss has been referred to above. In many parts of the world hookworm infestation is the most common cause of blood loss. There are recommended control programmes (intermittent antihelminthic medication at least twice yearly, control of faecal contamination of soil, use of simple shoes) for schoolchildren and women. These should be applied to preschool children as well, perhaps combined with iron supplementation (Stoltzfus *et al.*, 1997, 1998; Hopkins *et al.*, 1997). Bilharzia is less important as a cause of anaemia, trichuris and giardia have similarly been regarded as less frequent causes of iron deficiency as a population problem (de Morais *et al.*, 1996).

#### *Methods to achieve the strategy*

*Health education.* With a clear strategy implementation should be a simple matter of informing mothers what is best, but modification of eating customs and traditions is difficult.

Small-scale health education interventions have been successful, e.g. in a family practice in Bristol prevalence of microcytic anaemia at 13 months fell from 25% to 8% during a 2-year period, but enthusiasm waned because it had risen to 13% a further 2 years later (James *et al.*, 1993). Larger programmes have not been successful. In a project reaching about 500 children in a health district of Birmingham, about 30% of children in both the intervention and control groups were anaemic at 18 months of age (Childs *et al.*, 1997).

*Fiscal measures.* Consumption of suitable foods may be encouraged if their price to the consumer is reduced (sometimes free of charge) by subsidies from a government or a charity.

The outstanding example is the Women and Infants and Children Program in the U.S.A. (WIC). Iron-fortified infant formulas and weaning cereals are supplied free of charge to about a quarter of all infants. Since the programme was introduced the prevalence of iron deficiency anaemia has fallen considerably and is less than in many other countries (e.g. in U.S.A. the prevalence of IDA among 1–2-year-olds is 3%, Britain 12%; Looker *et al.*, 1997; Gregory *et al.*, 1995). A recent evaluation showed that those within the programme had less anaemia and a better iron status than those who were not (Owen & Owen, 1997). The British scheme, open to families on income support or job-seekers allowance, enables the mother to choose an infant formula (all of which are fortified in Britain) or whole cows' milk which contains little iron. Follow-on formulas, although fortified, are not included nor are 'solid' weaning foods.

Many other countries have subsidy schemes but many are based on milk alone, which, although excellent for energy, protein, calcium and riboflavine, does little to promote iron nutrition.

*Food fortification: infant formulas.* The main issue in iron fortification of infant formulas is quantity. Most formulas in the U.S.A. contain about 12 mg/l (1.8 mg/100 kcal) and most in Europe up to 7 mg/l (1.0 mg/100 kcal). In both continents formulas without added iron are allowed by the current regulations and in Scandinavia levels are around 4 mg/l (0.6 mg/100 kcal). There are proposals to add little or no iron to formulas consumed in the first 4–6 months of life (Wharton, 1989, 1996). (a) Total body iron increases little during this time, breast milk contains only small amounts of iron, and iron may have adverse effects on the faecal flora (Balmer & Wharton, 1991; Mevissen-Verhage *et al.*, 1985). (b) With higher fortification the absolute amount absorbed is only a little greater, leaving more unabsorbed iron in the gut lumen. (c) Young infants receiving an infant formula with no or small amounts of added iron in the first 4 months of life do not develop ID (Haschke *et al.*, 1993; Hernell & Lonnerdal, 1996). Nevertheless, almost all infant formulas used at this age do contain added iron.

From about 6 months of age more dietary iron becomes essential and a 'safety net of fortified foods' ensures a satisfactory intake (Wharton, 1986). The safety net usually includes a fortified formula but the appropriate level of fortification is unclear, e.g. continued use of a European infant formula (1 mg/100 kcal) or an American infant formula (1.8 mg/100 kcal) or introduction of a European style 'follow-on formula' (about 1.8 mg/100 kcal). Any of these options is preferable to the early introduction of ordinary cows' milk. Evidence is accumulating that even in formulas consumed in later infancy a level of fortification lower than used previously can be effective in maintaining adequate absorption and/or iron status, e.g. 8 mg (Fomon *et al.*, 1997), 3 mg (Haschke *et al.*, 1993) 2 mg (Walter *et al.*, 1998), but the periods of surveillance were for 3–6 months only and did not follow infants into the second year of life when anaemia is most common. Using radiolabelled iron infant formulas in adults, the Chilean group suggested fortification of 7 mg/l to provide 1 mg of absorbed iron (Hertrampf *et al.*, 1998).

A second issue is which qualities of an infant formula enhance iron status. Many studies have shown the positive effect of using iron-fortified formulas instead of cows' milk on iron status in infants >6 months old and in toddlers in the second year of life. It is not certain, however, to what extent this reflects solely the effect of a greater intake of iron, or is due also to 'other qualities' of an infant/follow-on formula such as the greater absorption of iron because of the higher vitamin C content, less inhibition of absorption because of the lower concentrations of protein, calcium and phosphorus (although one study found that the addition of calcium glycerophosphate did not adversely affect iron status; Dalton *et al.*, 1997), or less immunologically induced milk enteropathy and iron loss. Probably both the iron fortification and the 'other qualities' are operating. Three British studies of the use of follow-on formulas or cows' milk from the age of 6 months support that conclusion. ID was least in those receiving an iron fortified formula, more common in those receiving an unfortified formula and most in those on pasteurized cows milk (Daly *et al.*, 1996; Gill *et al.*, 1997; Stevens & Nelson, 1995).

*Food fortification: children's foods.* Iron is added to a variety of weaning foods, particularly cereals. The issues are the availability and the reactivity with other nutrients of the fortificant iron. Ferrous sulphate is relatively well absorbed but it catalyses the oxidation of unsaturated fats leading to rancidity, discoloration and flavour changes unless access to oxygen is limited (vacuum or nitrogen packing, rapid turnover times from fortification to consumption). Nevertheless fortification of wheat and maize flour with ferrous fumarate was acceptable to Venezuelan school children and reduced the prevalence of iron deficiency from 19% to 10% (Layrisse *et al.*, 1996). Powders of elemental iron, if finely ground, are well absorbed but similarly have a pro-oxidant effect; if less finely ground the oxidant effect is less but so is the absorption (Hurrell, 1997).

An alternative is to use haem iron as the fortificant, in effect adding blood to the food vehicle. This resulted in less ID and higher haemoglobin in Chile in older infants and school children (Hertrampf *et al.*, 1990; Walter *et al.*, 1993). A recent study in a small number of British 6-month-olds showed iron retention from a meat and cereal or a meat and vegetable dish was no higher if haem iron was added (retention 1–8 mg) than if ferrous sulphate were the fortificant (–1 to 6 mg) (Martinez *et al.*, 1998).

*Food fortification: adult foods and other vehicles.* Bread and breakfast cereals fortified with elemental iron are commonly consumed and breakfast cereals are also fortified with vitamin C. Sodium iron EDTA fortification is not inhibited by phytate, does not oxidize fats, and affects flavour less than ferrous sulphate, although discolouration remains a problem. Evaluation continues and it is not as yet licensed for general use. For general reviews of iron fortification see Hurrell (1997) and Gibson (1997).

Other foods which have been fortified with iron for consumption by children include water in Brazil (de Oliveira *et al.*, 1996), chocolate-flavoured milk also fortified with vitamin C in Jamaica (Davidsson *et al.*, 1998), and soft drinks in China (Cheng *et al.*, 1992).

#### *Iron supplementation*

Supplementation is generally not favoured for prevention because a toxic medicine is put into the household and anyway compliance is poor.

Regimens of oral iron every 5–7 d have been promoted. Compliance is better, and in field studies in developing countries they are as effective as a daily dose probably because a daily dose saturates the enterocyte, blocking absorption of the next doses for a few days. Viteri (1997, 1998) and Solomons (1997) have reviewed this approach. Most evidence relates to animal studies or adults, particularly during pregnancy, but some experiences in preschool children are described, e.g. in Bolivia (Berger *et al.*, 1997), China (Liu & Liu, 1996), Indonesia (Schultink *et al.*, 1995) and Vietnam (Thu *et al.*, 1999), and also in Indonesian school-children in whom an improvement in growth as well as iron status was noted (Angeles-Agadeppa *et al.*, 1997; Soemantri *et al.*, 1997). Controversy remains about this intermittent approach. Cook & Reddy (1995) found the absorption of radiolabelled iron by adult volunteers was

similar whether daily or intermittent doses were given and they questioned the desirability or need for intermittent regimens compared to the well-tried daily method. More detailed discussion can be found in the correspondence following the publication of the paper (Viteri, 1996; Cook, 1996). Coffee drinking reduces the effectiveness of supplementation (increase in serum ferritin) in Guatemalan 1–2-year-olds (Dewey *et al.*, 1997). Presumably tea could have a similar effect. A third of British toddlers drink tea. Parenteral iron given at 2 months increases the risk of malarial parasitaemia but oral iron was used safely in Tanzania, reducing the prevalence of severe anaemia and not increasing the frequency of malaria (Menendez *et al.*, 1997).

The use of micronutrient supplements in developing countries is being actively considered by UNICEF and USAID. There is a possibility of interaction of different minerals in multimicronutrient supplements. A zinc supplement given in water depresses the absorption of iron, but not when both minerals are presented in food, e.g. a hamburger (Rossander-Hulten *et al.*, 1991). The interaction may be a further reason for giving iron in a food vehicle (fortification) or singly if given as a medicine.

#### *Caution with prevention programmes*

Ideally only those requiring extra iron would receive it. There is some association between raised measurements of iron nutrition, heart disease, and cancer in adults, but no firm conclusions can be reached and the cause of the raised measurements may reflect inflammation rather than a high intake (see the major reviews referred to earlier: British Nutrition Foundation, 1995; Hallberg & Asp, 1996).

Nevertheless the possibility of adverse effects of iron programmes in children should be considered. If an individual receives more dietary iron than they need the control mechanisms make excessive iron absorption unlikely unless there is increased erythropoiesis or dyserythropoiesis (e.g. in thalassaemia) or as yet undiagnosed haemochromatosis is present. What is the effect of any unnecessary unabsorbed iron? Lactoferrin in breast milk is an important antibacterial agent in the intestine (at least *in vitro*; the evidence *in vivo* is unclear), but if saturated with iron the effect is lost. Despite the lack of evidence *in vivo* it is therefore preferable to avoid iron supplements in babies receiving breast milk in the first 6 months of life. The addition of added iron to an infant formula – which of course does not contain lactoferrin – is not apparently an important factor in the pathogenesis of intestinal infection in bottle-fed infants, nor in systemic infection (Walter *et al.*, 1997).

## CONCLUSIONS

Iron deficiency anaemia is common in childhood, particularly in toddlers living in inner city areas or children of immigrants. Adolescents also experience the problem but less frequently. Although the differential diagnosis of microcytic anaemia includes hereditary causes and inflammation as well as iron deficiency, diagnosis is usually not difficult.

Strategies for prevention are as for any other nutrient

deficiency, i.e. screening, health education, fiscal measures, food fortification, and supplementation. Perinatal factors and avoidance of blood loss also need attention. Food fortification is the most effective method of prevention, but giving extra amounts of a nutrient to those who do not need it is undesirable. There seems little need to give extra iron (by fortification or supplementation) during the first 4–6 months of life. From then good dietary sources of available iron are essential. Since many children do not receive these sources in sufficient amounts there is a strong public health argument for using a safety net of fortified foods particularly when they can be 'targeted' by using food vehicles consumed by vulnerable groups.

MRC Childhood Nutrition  
Research Unit,  
Institute of Child Health,  
London

BRIAN A. WHARTON

## REFERENCES

- Abshire, T.C. (1996) The anemia of inflammation: a common cause of childhood anemia. *Pediatric Clinics of North America*, **43**, 623–637.
- Angeles-Agdeppa, I., Schultink, W., Sastramidjojo, S., Gross, R. & Karyadi, D. (1997) Weekly micronutrient supplementation to build iron stores in female Indonesian adolescents. *American Journal of Clinical Nutrition*, **66**, 177–183.
- Aoki, Y., Urata, G. & Takakura, F. (1973) Delta aminolevulinic acid synthetase in erythroblasts of patients with primary sideroblastic anaemia. *Acta Haematologica Japonica*, **36**, 74–75.
- Aslan, Y., Erduran, E., Mocan, H., Gedik, Y., Okten, A., Soylu, H. & Deger, O. (1997) Absorption of iron from grape-molasses and ferrous sulfate: a comparative study in normal subjects and subjects with iron deficiency anemia. *Turkish Journal of Pediatrics*, **39**, 465–471.
- Balmer, S.E. & Wharton, B.A. (1991) Diet and faecal flora in the newborn: iron. *Archives of Diseases of Childhood*, **69**, 95–98.
- Bannerman, R.F. (1981) Of mice and men and microcytes. *Journal of Pediatrics*, **98**, 760–762.
- Beghetti, M., Mermillod, B. & Halperin, D.S. (1993) Blue sclerae: a sign of iron deficiency anemia in children? *Pediatrics*, **91**, 1195–1196.
- Benjamin, J.T., Dickens, M.D., Ford, R.F., Hawkes, D.L., Machen, C.W. & Perriello, V.A. (1991) Normative data of hemoglobin concentration and free erythrocyte protoporphyrin in a private pediatric practice: a 1990 update. *Clinical Pediatrics*, **30**, 74–76.
- Berger, J., Aguayo, V.M., Tellez, W., Lujan, C., Traissac, P. & San-Miguel, J.L. (1997) Weekly iron supplementation is as effective as 5 day per week iron supplementation in Bolivian school children living at high altitude. *European Journal of Clinical Nutrition*, **51**, 381–386.
- Borigato, E.V. & Martinez, F.E. (1998) Iron nutritional status is improved in Brazilian preterm infants fed food cooked in iron pots. *Journal of Nutrition*, **128**, 855–859.
- Boulter, M.N. & Needlman, R. (1996) Use of diet history in the screening of iron deficiency. *Pediatrics*, **98**, 1138–1142.
- British Nutrition Foundation (1995) *Iron: Nutritional and Physiological Significance*. Chapman & Hall, London.
- Brock, J.H., Halliday, J.W., Pippard, M.J. & Powell, M.W. (1994) *Iron Metabolism in Health and Disease*. Saunders, London.
- Buchanan, G.R. & Sheehan, R.G. (1981) Malabsorption and defective utilisation of iron in three siblings. *Journal of Pediatrics*, **98**, 725–728.
- Cazzola, M., Ponchio, L., de-Benedetti, F., Ravelli, A., Rosti, V., Beguin, Y., Invernizzi, R., Barosi, G. & Martini, A. (1996) Defective iron supply for erythropoiesis and adequate endogenous erythropoietin production in the anemia associated with systemic onset juvenile chronic arthritis. *Blood*, **87**, 482–483.
- Centres for Disease Control and Prevention (1998) Recommendations to prevent and control iron deficiency in the United States. *Morbidity and Mortality Weekly Report*, **47**, 1–29.
- Cheng, X.C., Wang, W.G., Yan, H.C., Yin, T.A. & Xu, Q.M. (1992) Studies on iron deficiency anemia, rickets and zinc deficiency and their prevention among Chinese preschool children. *Progress in Food and Nutrition Science*, **16**, 263–267.
- Childs, F., Aukett, A., Darbyshire, P., Ilett, S. & Livera, L.N. (1977) Dietary education and iron deficiency anaemia in the inner city. *Archives of Diseases of Childhood*, **76**, 144–147.
- Choi, Y.S. & Reid, T. (1998) Anemia and red cell distribution width at the 12 month well baby examination. *Southern Medical Journal*, **91**, 372–374.
- Colomer, J., Colomer, C., Gutierrez, Jubert, A., Nolasco, A., Donat, J., Fernandez-Delgado, R., Donat, F. & Alvarez-Dardet, C. (1990) Anaemia during pregnancy as a risk factor for infant iron deficiency: report from the Valencia Infant Anaemia Cohort (VIAC) study. *Paediatric Perinatal Epidemiology*, **4**, 196–204.
- Cook, J.D. (1996) Reply to F. E. Viteri. *American Journal of Clinical Nutrition*, **63**, 611–612.
- Cook, J.D. & Reddy, M.B. (1995) Efficacy of weekly compared with daily iron supplementation. *American Journal of Clinical Nutrition*, **62**, 117–120.
- Cooley, T.B. (1945) A severe form of hereditary anaemia with eliptocytosis: interesting sequence of splenectomy. *American Journal of Medical Science*, **209**, 561–568.
- Dallman, P.R., Looker, A.C., Johnson, C.L. & Carroll, M. (1996) Influence of age on laboratory criteria for the diagnosis of iron deficiency in infants and children. *Iron Nutrition in Health and Disease* (ed. by L. Hallberg and N. G. Asp), pp. 65–74. John Libbey, London.
- Dalton, M.A., Sargent, J.D., O'Connor, G.T., Olmstead, E.M. & Klein, R.Z. (1997) Calcium and phosphorus supplementation of iron fortified infant formula: no effect on iron status of healthy full term infants. *American Journal of Clinical Nutrition*, **65**, 921–926.
- Daly, A., MacDonald, A., Aukett, A., Williams, J., Wolf, A., Davidson, J. & Booth, I.W. (1996) Prevention of anaemia in inner city toddlers by an iron supplemented cows milk formula. *Archives of Diseases in Childhood*, **75**, 9–16.
- Davidsson, L., Walczyk, T., Morris, A. & Hurrell, R.F. (1998) Influence of ascorbic acid on iron absorption from an iron-fortified, chocolate-flavored milk drink in Jamaican children. *American Journal of Clinical Nutrition*, **67**, 873–877.
- De Moraes, M.B., Suzuki, H.U., Corral, J.N., Machado, N.L. & Neto, U.F. (1996) Asymptomatic giardiasis does not affect iron absorption in children with iron deficiency anemia. *Journal of American College of Nutrition*, **15**, 434–438.
- de Oliveira, J.E., Scheid, M.M., Desai, I.D. & Marchini, S. (1996) Iron fortification of domestic drinking water to prevent anemia among low socioeconomic families in Brazil. *International Journal of Food Science and Nutrition*, **47**, 213–219.
- Department of Health (1989) *The Diets of British School Children*. Reports on Health and Social Subjects, No. 36. HMSO, London.
- Department of Health (1994) *Weaning and the Weaning Diet*. Report on Health and Social Subjects, No. 45. HMSO, London.
- De Vizia, B., Poggi, V., Conenna, R., Fiorillo, A. & Scippa, L. (1992) Iron absorption and iron deficiency in infants and children with gastrointestinal diseases. *Journal of Pediatric Gastroenterology and Nutrition*, **14**, 21–26.

- Dewey, K.G., Cohen, R.J., Rivera, L.L. & Brown, K.H. (1998) Effects of age of introduction of complementary foods on iron status of breast fed infants in Honduras. *American Journal of Clinical Nutrition*, **67**, 878–884.
- Dewey, K.G., Romero-Abal, M.E., Quan-de-Serrano, J., Bulux, J., Peerson, J.M. & Eagle, P. (1997) Effects of discontinuing coffee intake on iron status of iron deficient Guatemalan toddlers: a randomised intervention study. *American Journal of Clinical Nutrition*, **66**, 168–176.
- d'Onofrio, G., Zini, G., Ricerca, B.M., Mancini, S. & Mango, G. (1992) Automated measurement of red blood cell microcytosis and hypochromia in iron deficiency and beta-thalassaemia trait. *Archives of Pathological Laboratory Medicine*, **116**, 84–89.
- Doyle, W., Jenkins, S., Crawford, M.A. & Puvandendran, K. (1994) Nutritional status of school children in an inner city area. *Archives of Diseases in Childhood*, **70**, 376–381.
- Engelmann, M.D., Sandstrom, B. & Michaelsen, K.F. (1998) Meat intake and iron status in late infancy: an intervention study. *Journal of Pediatric Gastroenterology and Nutrition*, **26**, 26–33.
- Fomon, S.J. (1993) *Nutrition of Normal Infants*, pp. 239–260. Mosby, St Louis.
- Fomon, S.J., Ziegler, E.E., Serfass, R.E., Nelson, S.E. & Frantz, J.A. (1997) Erythrocyte incorporation of iron is similar in infants fed formulas fortified with 12 mg/L or 8 mg/L of iron. *Journal of Nutrition*, **127**, 83–88.
- Fuchs, G.J., De Weir, M., Hutchinson, S., Sundeen, M., Schwartz, S. & Suskind, R. (1993a) Gastrointestinal blood loss in older infants: impact of cows milk versus formula. *Journal of Paediatric Gastroenterology and Nutrition*, **16**, 4–9.
- Fuchs, G.J., Farris, R.P., De Weir, M., Hutchinson, S.W., Warrior, R., Doucet, H. & Suskind, R. (1993) Iron status and intake of older infants fed formula versus cows milk with cereal. *American Journal of Clinical Nutrition*, **58**, 343–348.
- Geethanath, R.M., Ramji, S., Thirupuram, S. & Rao, Y.N. (1997) Effect of timing of cord clamping on the iron status on infants at 3 months. *Indian Pediatrics*, **34**, 103–106.
- Gibson, R.S. (1997) Technological approaches to combating iron deficiency. *European Journal of Clinical Nutrition*, **51**, (Suppl. 4), S25–S27.
- Gill, D.G., Vincent, S. & Segal, D.S. (1997) Follow-on formula in the prevention of iron deficiency: a multicentre study. *Acta Paediatrica*, **86**, 683–689.
- Goedseels, J., DeCaluwe, J.P. & Alexander, M. (1997) Congenital sideroblastic anemia in an infant. *Archives of Pediatrics*, **4**, 979–982.
- Goya, M., Miyazaki, S., Kodate, S. & Ushio, B. (1972) A family of congenital atransferrinaemia. *Blood*, **40**, 239–245.
- Graham, E.A., Felgenhauer, J., Detter, J.C. & Labbe, R.F. (1996) Elevated zinc protoporphyrin associated with thalassaemia trait and hemoglobin E. *Journal of Pediatrics*, **129**, 105–110.
- Graham, E.A.M., Carlson, T.H., Sodergren, K.K., Detter, J.C. & Labbe, R.F. (1997) Delayed bottle weaning and iron deficiency in southeast Asian toddlers. *Western Journal of Medicine*, **167**, 10–14.
- Grajeda, R., Perez-Escamilla, R. & Dewey, K.G. (1997) Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 months of age. *American Journal of Clinical Nutrition*, **65**, 425–431.
- Gregory, J.R., Collins, D.J. & Davies, P.S.W. (1995) *National Diet and Nutrition Survey: Children aged 1.5–4.5 years*, Volume 1. HMSO, London.
- Gujural, S. & Gopaldas, T. (1995) Risk factors of nutritional blindness and determinants of a successful vitamin A prophylaxis programme. *Indian Pediatrics*, **32**, 199–205.
- Hallberg, L. & Asp, N.G. (1996) *Iron Nutrition in Health and Disease*. John Libbey, London.
- Hammad, T.A., Sexton, M. & Langenberg, P. (1996) Relationship between blood lead and dietary iron intake in preschool children: a cross sectional study. *Annals of Epidemiology*, **6**, 30–33.
- Hartfield, D.S., Lowry, N.J., Keene, D.L. & Yager, J.Y. (1997) Iron deficiency: a cause of stroke in infants and children. *Pediatric Neurology*, **16**, 50–53.
- Hartman, K.R. & Barker, J.A. (1996) Microcytic anemia with iron malabsorption: an inherited disorder of iron metabolism. *American Journal of Hematology*, **51**, 269–275.
- Haschke, F., Vanura, H., Male, C., Owen, G., Pietschnig, B., Schuster, E., Krobath, E. & Huemer, C. (1993) Iron nutrition and growth of breast and formula fed infants during the first 9 months of life. *Journal of Pediatric Gastroenterology and Nutrition*, **16**, 151–156.
- Haymes, E.M. & Lamanca, J.J. (1989) Iron loss in runners during exercise: implications and recommendations. *Sports Medicine*, **7**, 277–285.
- Heaton, J. M., Blair, R.L., Shadbolt, C. & Christmas, H. (1991) An assessment of the incidence of iron deficiency in paediatric otolaryngology inpatients. *Journal of Laryngology and Otolaryngology*, **105**, 1021–1024.
- Hernell, O. & Lonnerdal, B. (1996) Iron requirements and prevalence of iron deficiency in the first 6 months of life. *Iron Nutrition in Health and Disease* (ed. by L. Hallberg and N. G. Asp), pp. 129–136. John Libbey, London.
- Hertrampf, E., Olivares, M., Pizarro, F. & Walter, T. (1998) High absorption of fortification iron from current infant formulas. *Journal of Pediatric Gastroenterology and Nutrition*, **27**, 425–430.
- Hertrampf, E., Olivares, O., Pizarro, F., Walter, T., Cavazzo, M., Ileresi, G., Llaguno, S., Chadud, P. & Stekel, A. (1990) Haemoglobin fortified cereal: a source of available iron in breast fed infants. *European Journal of Clinical Nutrition*, **44**, 793–798.
- Huebers, H.A., Beguin, Y., Pootrakul, P., Einspahr, D. & Finch, C.A. (1990) Intact transferrin receptors in human plasma and their relation to erythropoiesis. *Blood*, **75**, 102–107.
- Hetzel, T.M. & Losek, J.D. (1998) Unrecognised severe anemia in children presenting with respiratory distress. *American Journal of Emergency Medicine*, **16**, 386–389.
- Hinchcliffe, R.F. & Helliwell, M.M. (1993) *Red Cells in Children*, pp. 3–28. Bayer Diagnostics, Basingstoke.
- Hopkins, R.M., Gracey, M.S., Hobbs, R.P., Spargo, R.M., Yates, M. & Thompson, R.C. (1997) The prevalence of hookworm infection, iron deficiency and anaemia in an aboriginal community in north west Australia. *Medical Journal of Australia*, **166**, 241–244.
- Hurrell, R.F. (1997) Preventing iron deficiency through food fortification. *Nutrition Reviews*, **55**, 210–222.
- James, J., Bailwaard, T., Lawson, P. & Laing, G. (1993) Treatment of iron deficiency anaemia with iron in children. *Lancet*, **341**, 572.
- Kim, K.K., Cheong, W.S., Jun, Y.H., Choi, J.W. & Son, B.K. (1996) Red blood cell indices and iron status according to feeding practice in infants and young toddlers. *Acta Paediatrica*, **85**, 139–144.
- Kivivuori, S.M., Anttila, R., Viinikka, L., Pesonen, K. & Siimes, M.A. (1993) Serum transferrin receptor for assessment of iron status in healthy pre pubertal and early pubertal boys. *Pediatric Research*, **34**, 97–299.
- Kling, P.J., Roberts, R.A. & Widness, J.A. (1998) Plasma transferrin receptor levels and indices of erythropoiesis and iron status in healthy term infants. *Journal of Pediatric Hematology and Oncology*, **20**, 309–314.
- Kuiper-Kramer, E.P., Baerts, W., Bakker, R., van-Eyck, J., van-Raan, J. & van-Eijk, H.G. (1998) Evaluation of the iron status of the newborn by soluble transferrin receptors in serum. *Clinical Chemical Laboratory Medicine*, **36**, 17–21.

- Kuizon, M.D., Madriaga, J.D., Desnacido, J.A., Cheong, R.L. & Perlas, L.A. (1996) Iron status of Filipino infants and preschoolers using plasma ferritin and transferrin receptor levels. *Southeast Asian Journal of Tropical Medicine and Public Health*, **27**, 343–349.
- Lawson, M.S., Thomas, M. & Hardiman, A. (1998) Iron status of Asian children aged 2 years living in England. *Archives of Diseases in Childhood*, **78**, 420–426.
- Layrisse, M., Chaves, J.E., Mendez-Castellano, J., Bosch, V., Tropper, E., Bastardo, B. & Gonzalez, E. (1996) Early response to the effect of iron fortification in the Venezuelan population. *American Journal of Clinical Nutrition*, **64**, 903–907.
- Linpisarn, S., Tienboon, P., Promtet, N., Putsyainunt, P., Santawanpat, S. & Fuchs, G. (1996) Iron deficiency and anaemia in children with a high prevalence of haemoglobinopathies: implications for screening. *International Journal of Epidemiology*, **25**, 1262–1266.
- Liu, X.N. & Liu, P.Y. (1996) The effectiveness of weekly iron supplementation regimen in improving the iron status of Chinese children and pregnant women. *Biomedical and Environmental Science*, **9**, 341–347.
- Lonnerdal, B. (1990) *Iron Metabolism in Infants* (ed. by B. Lonnerdal), pp. 1–85. CRC Press, New York.
- Looker, A.C., Dallman, P.R., Carroll, M.D., Gunter, E.W. & Johnson, C.L. (1997) Prevalence of iron deficiency in the United States. *Journal of the American Medical Association*, **26**, 973–976.
- Lynch, S.R. (1997) Interaction of iron with other nutrients. *Nutrition Reviews*, **55**, 102–110.
- Markowitz, M.E., Clemente, I. & Rosen, J.F. (1997) Children with moderately elevated blood lead levels: a role for other diagnostic tests? *Environmental Health Perspectives*, **105**, 1084–1088.
- Martinez, C., Fox, T., Eagles, J. & Fairweather-Tait, S.J. (1998) Evaluation of iron bioavailability in infant weaning foods with haem concentrate. *Journal of Pediatric Gastroenterology*, **27**, 419–424.
- Mates, M., Heyd, J., Souroujon, M., Ben-Sasson, A., Manny, N. & Hershko, C. (1995) The haematologist as watchdog of full blood count. *Quarterly Journal of Medicine*, **88**, 333–339.
- Menendez, C., Kahigwa, E., Hirt, R., Vounatsou, P., Aponte, J.J., Font, F., Acosta, C.J., Schellenberg, D.M., Galindo, C.M., Kimario, J., Urassa, H., Brabin, B., Smith, T.A., Kitua, A.Y., Tanner, M. & Alonso, P.L. (1997) Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet*, **350**, 844–850.
- Mevissen-Veharge, E.A.E., Marcellis, J.H. & Harmsen-van Amerongen, C.M. (1985) Effect of iron on neonatal gut flora during the first three months of life. *European Journal of Clinical Microbiology*, **4**, 273–278.
- Mills, A. & Tyler, H. (1992) *Food and Nutrition Intakes of British Infants aged 6–12 months*. HMSO, London.
- Mira, M., Alperstein, G., Karr, M., Ranmuthagala, G., Causer, J., Niec, A. & Lilburne, A.M. (1996) Haem iron intake in 12–36 month old children depleted in iron: case–control study. *British Medical Journal*, **312**, 881–883.
- Moynihan, P.J., Anderson, C. & Adamson, A.J. (1994) Dietary sources of iron in English adolescents. *Journal of Human Nutrition and Dietetics*, **7**, 225–230.
- Olcay, L., Ozer, S., Gurgey, A., Saraclar, M., Ozme, S., Bilgic, A., Ozcutlu, S. & Celiker, A. (1996) Parameters of iron deficiency in children with cyanotic congenital heart disease. *Pediatric Cardiology*, **17**, 150–154.
- Oski, F.A. (1993) Iron deficiency in infancy and childhood. *New England Journal of Medicine*, **29**, 190–193.
- Oski, F.A., Honig, A.S., Helu, B. & Howanitz, P. (1983) Effect of iron therapy on behaviour performance in non-anemic iron deficient infants. *Pediatrics*, **71**, 677–880.
- Owen, A.L. & Owen, G.M. (1997) Twenty years of WIC: a review of some effects of the program. *Journal of the American Dietetic Association*, **7**, 777–782.
- Petersen, K.M., Parkinson, A.J., Nobmann, E.D., Bulkow, L., Yip, R. & Mokdad, A. (1996) Iron deficiency anemia among Alaskan Natives may be due to fecal loss rather than inadequate intake. *Journal of Nutrition*, **126**, 2774–2783.
- Phillips, M.R., Zaheer, S. & Drugas, G.T. (1998) Gastric trichobezoar: case report and literature review. *Mayo Clinic Proceedings*, **73**, 653–656.
- Pisacane, A., De Vizia, B., Valiante, A., Vaccaro, F., Russo, M., Grillo, G. & Giustardi, A. (1995) Iron status in breast-fed infants. *Journal of Pediatrics*, **127**, 429–431.
- Robertsson, J.D., Maughan, R.J. & Davidsson, R.L.J. (1987) Faecal blood loss in response to exercise. *British Medical Journal*, **295**, 303–305.
- Rossander-Hulten, L., Brune, M., Sandstrom, B., Lonnerdal, B. & Hallberg, L. (1991) Comparative inhibition of iron absorption by manganese and zinc in humans. *American Journal of Clinical Nutrition*, **54**, 152–156.
- Ruff, H.A., Markowitz, M.E., Bijur, P.E. & Rosen, J.F. (1996) Relationships among blood lead levels, iron deficiency, and cognitive development in two year old children. *Environmental Health Perspectives*, **104**, 180–185.
- Sargent, J.D., Brown, M.J., Freeman, J.L., Bailey, A., Goodman, D. & Freeman, D.H., Jr (1995) Childhood lead poisoning in Massachusetts communities: its association with sociodemographic and housing characteristics. *American Journal of Public Health*, **85**, 528–534.
- Sargent, J.D., Stukel, T.A., Dalton, M.A., Freeman, J.L. & Brown, M.J. (1996) Iron deficiency in Massachusetts communities: socioeconomic and demographic risk factors among children. *American Journal of Public Health*, **86**, 544–550.
- Schultink, W., Gross, R., Gliwitski, M., Karyadi, D. & Matulesi, P. (1995) Effect of daily vs twice weekly iron supplementation in Indonesian pre-school children with low iron status. *American Journal of Clinical Nutrition*, **61**, 111–115.
- Shahidi, N.T., Nathan, D.E. & Diamond, L.K. (1964) Iron deficiency anemia associated with error of iron metabolism. *Journal of Clinical Investigation*, **43**, 510–521.
- Sherriff, A., Emond, A., Hawkins, N. & Golding, J. (1999) Haemoglobin and ferritin concentration in children aged 12 and 18 months. *Archives of Disease in Childhood*, **80**, 153–157.
- Skikne, B.S., Flowers, C.H. & Cook, J.D. (1990) Serum transferrin receptors: a quantitative measure of tissue iron deficiency. *Blood*, **75**, 1870–1876.
- Siegal, R.M. & LaGrone, D.H. (1994) The use of zinc protoporphyrin in screening young children for iron deficiency. *Clinical Pediatrics*, **33**, 473–479.
- Soemantri, A.G., Hapsari, D.E., Susanto, J.C., Rohadi, W., Tamam, P., Irawan, P.W. & Sugianto, A. (1997) Daily and weekly iron supplementation and physical growth of school age Indonesian children. *Southeast Asian Journal of Tropical Medicine and Public Health*, **28**, (Suppl. 2), 69–74.
- Solomons, N.W. (1997) Weekly versus daily oral iron administration: are we asking the right questions? *Nutrition Reviews*, **55**, 141–142.
- Southon, S., Wright, A.J.A. & Finglas, P.M. (1994) Dietary intake and micronutrient status of adolescents: effect of vitamin and trace element supplementation in tests of verbal and nonverbal intelligence. *British Journal of Nutrition*, **71**, 897–918.
- Spitzer, N., Newcomb, T.F. & Noyes, W.D. (1996) Pyridoxine responsive hypolipidemia and hypocholesterolemia in a patient with pyridoxine responsive anaemia. *New England Journal of Medicine*, **274**, 772–775.

- Stahlberg, M.R., Savilahti, E. & Siimes, M.A. (1991) Iron deficiency in coeliac disease is mild and it is detected and corrected by gluten free diet. *Acta Paediatrica Scandinavica*, **80**, 190–193.
- Stevens, D. & Nelson, A. (1995) The effect of iron in formula milk after 6 months of age. *Archives of Disease in Childhood*, **73**, 216–220.
- Stoltzfus, R.J., Albonico, M., Chwaya, H.M., Tielsch, J.M., Schulze, K.J. & Savioli, L. (1998) Effects of the Zanzibar deworming program on iron status of children. *American Journal of Clinical Nutrition*, **68**, 179–186.
- Stoltzfus, R.J., Dreyfuss, M.L., Chwaya, H.M. & Albonico, M. (1997) Hookworm control as a strategy to prevent iron deficiency. *Nutrition Reviews*, **55**, 223–232.
- Stordy, B.J., Redfern, A.M. & Morgan, J.B. (1995) Healthy eating for infants: mothers' actions. *Acta Paediatrica*, **84**, 733–741.
- Strauss, M.B. (1993) Anemia of infancy from maternal iron deficiency in pregnancy. *Clinical Investigation*, **12**, 345–353.
- Tatala, S., Svanberg, U. & Mduma, B. (1998) Low dietary iron availability is a major cause of anemia: a nutrition survey in the Lindi District of Tanzania. *American Journal of Clinical Nutrition*, **68**, 171–178.
- Thaver, I.H. & Baig, L. (1994) Anaemia in children: Part 1. Can simple observations by primary care provider help in diagnosis? *Journal of the Pakistani Medical Association*, **44**, 282–284.
- Thu, B.D., Schultink, W., Dillon, D., Gross, R., Leswara, N.D. & Khoi, H.H. (1999) Effect of daily and weekly micronutrient supplementation on micronutrient deficiencies and growth in young Vietnamese children. *American Journal of Clinical Nutrition*, **69**, 80–86.
- Underwood, B.A. & Arthur, P. (1996) The contribution of vitamin A to public health. *FASEB Journal*, **10**, 1040–1048.
- Virtanen, M.A., Viinika, L.U., Virtanen, M.K.G., Svahn, J.C.E., Antilla, R.M., Krusius, T., Cook, J.D., Axelsson, I.E.M., Raiha, N.C.R. & Siimes, M.A. (1999) Higher concentration of serum transferrin receptor in children than in adults. *American Journal of Clinical Nutrition*, **69**, 256–260.
- Viteri, F. (1996) Weekly compared with daily iron supplementation. *American Journal of Clinical Nutrition*, **63**, 610–611.
- Viteri, F. (1997) Iron supplementation for the control of iron deficiency in populations at risk. *Nutrition Reviews*, **55**, 195–209.
- Viteri, F.E. (1998) A new concept in the control of iron deficiency: community based preventive supplementation of at risk groups by the weekly intake of iron supplements. *Biomedical and Environmental Sciences*, **11**, 46–60.
- Walter, T., Hertrampf, E., Pizarro, F., Olivares, M., Llaguno, S., Letelier, A., Vega, V. & Stekel, A. (1993) Effects of bovine-hemoglobin-fortified cookies on iron status in schoolchildren: a nationwide program in Chile. *American Journal of Clinical Nutrition*, **57**, 190–194.
- Walter T., Olivares, M.O., Pizarro, F. & Munoz, C. (1997) Iron, anaemia and infection. *Nutrition Reviews*, **55**, 111–124.
- Walter, T., Pino, P., Pizarro, F. & Lozoff, B. (1998) Prevention of iron deficiency anemia: comparison of high and low iron formulas in term healthy infants after six months of life. *Journal of Pediatrics*, **132**, 635–640.
- Walters, M.C. & Abelson, H.T. (1996) Interpretation of the complete blood count. *Pediatric Clinics of North America*, **43**, 599–622.
- Wharton, B.A. (1986) Food for the weanling. *Acta Paediatrica*, Suppl. **323**, 95–99.
- Wharton, B.A. (1989) Iron nutrition in childhood: the interplay of genes, development and environment. *Acta Paediatrica*, Suppl. **361**, 5–11.
- Wharton, B.A. (1996) Nutrient deficiency in the breast fed infant. *Recent Developments in Infant Nutrition* (ed. by J. G. Bindels, A. C. Goedhart and H. K. A. Visser), pp. 260–271. Kluwer Academic, Dordrecht.
- Wharton, B.A. (1999a) Iron deficiency. *Textbook of Pediatric Hematology* (eds Lilleyman, Hahn & Blanchard), pp. 127–144. Churchill Livingstone, London.
- Wharton, B.A. (1999b) Low plasma vitamin D in Asian toddlers in Britain. *British Medical Journal*, **318**, 2–3.
- White, A., Freeth, S. & O'Brien, M. (1992) *Infant Feeding 1990*. HMSO, London.
- Worwood, M. (1995) Measurement of iron status. *Iron: Nutritional and Physiological Significance*, pp. 33–41. Chapman and Hall, London.
- Worwood, M. (1997) Influence of disease on iron status. *Proceedings of the Nutrition Society*, **56**, 409–419.
- Yip, R., Stoltzfus, R.J. & Simmons, W.K. (1996) Assessment of the prevalence of the nature of iron deficiency for populations: the utility of comparing haemoglobin distributions. *Iron Nutrition in Health and Disease* (ed. by L. Hallberg and N. G. Asp), pp. 31–48. John Libbey, London.
- Ziegler, E.E. & Fomon, S.J. (1996) Strategies for the prevention of iron deficiency: iron in infant formulas and baby foods. *Nutrition Reviews*, **54**, 348–354.
- Ziegler, E.E., Fomon, S.H., Nelson, S.E., Rebouche, J., Edwards, B.B., Rogers, R.R. & Lehman, L.J. (1990) Cow milk feeding in infancy: further observations on blood loss from the gastrointestinal tract. *Journal of Pediatrics*, **116**, 11–18.

**Keywords:** iron deficiency, children.