

Review article

The remedying of iron deficiency: what priority should it have?

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Fe deficiency is considered to be the commonest of nutritional deficiencies worldwide. Adverse effects are stated to include lower growth rate and impaired cognitive scores in children and poor pregnancy outcome and lower working capacity in adults. In the present review, Fe intake, stores of the element, the magnitude of deficiencies and the benefits from interventions, as reflected in the results of clinical trials, are discussed. Because of inadequacies of knowledge in numerous respects, more information is needed regarding the extent to which clinical trials relate to public health realities, before introducing regional or national supplementation programmes. While Fe supplements are needed in certain groups, and in particular regions, increased dietary intakes could be supplied by food fortification, as well as by individual improvements in intake.

Iron: Deficiency stigmata: Supplementation

According to the World Health Organization (WHO), Fe deficiency is the commonest of deficiency diseases worldwide (DeMaeyer *et al.* 1989). In children, disadvantages range from lower growth rate to impaired cognitive development, while in adults poor pregnancy outcome and lower work capacity may be found (Yip, 1994). The associated ill-effects have been described as 'devastating' (Scrimshaw, 1991) and, in some contexts, as 'irreversible' (Lozoff *et al.* 1991). Because of the universal commonness of the deficiency it would be expected that there would be ample data, past and updated, in both developed and developing populations, which would portray accurately not only the epidemiology of the deficiency but the intensity of its stigmata, its sequelae, the interventions undertaken and the precise benefits to health accruing, both currently and in the future, from supplementation to individuals and communities. Unfortunately, in all these various respects, knowledge is limited in both developed and developing populations (Walker *et al.* 1994). Studies have been almost wholly of the randomized clinical type, which have numerous limitations (Block, 1995). Moreover, few attempts have been made to learn to what extent benefits from trials are identifiable in 'real life' (Kretchmer *et al.* 1996). One authority has gone so far as to assert that 'successful intervention programmes in the last decade have been virtually non-existent' (Beard, 1996).

In the present review, the topics discussed are: Fe intake, Fe stores and markers, the magnitude of Fe-deficiency stigmata in children and adults, the extent to which clinical trials relate to public health programmes, the need for more specific definition of deficiency sequelae, and means of increasing intake of the element.

Iron intake

The daily recommended dietary allowance (National Academy of Sciences, 1990) for Fe (mg) is for children 10–12, for men 10, women 15, and in pregnancy 30. Additionally, a recent recommendation is that the allowance for menstruating women should be raised to 20 mg daily (Hallberg & Rossander-Hulthén, 1991). While allowances must not be confused with physiological needs, it would appear that in Western populations, the intakes of a large proportion are low, and need supplementation. In developing populations, understandably, the proportion with low intakes is higher; moreover, in such populations there is the need for additional Fe in areas where infections which involve blood destruction, as in the case of malaria, and blood loss with helminths, such as hookworm, are endemic (Fleming, 1989).

Examples of intakes of Fe are given in Table 1. As will be apparent, ranges are wide. For example, in a group of children of 7–8 years in the UK, intake averaged 9.4 mg daily (Ruxton & Kirk, 1996), while in a group aged 12–14 years, mean daily intakes were higher at 12.3 and 9.6 mg for boys and girls respectively. It was claimed that intakes in adolescents have been declining in the last two decades (Nelson *et al.* 1993); yet intakes can be high, as among vegetarians and omnivores in New Zealand, whose respective averages were reported as 20.2 and 17.4 mg/d for men, and 15.5 and 13.5 mg/d for women (Alexander *et al.* 1994).

In developing populations there are also wide ranges. Thus, the daily intake of middle-aged African men in Cape Town was reported to average 10 mg, and for women, 7 mg (Bourne *et al.* 1993). In contrast, in rural African populations in contexts where large amounts of vegetables and fruit are eaten, Fe intakes can be unusually high. As an example, in those living in Northern Province, South Africa, mean daily intakes were reported as 21.4 and 21.6 mg for men and women respectively (Vorster *et al.* 1994).

With respect to the bioavailability of the element, haem-Fe from mainly animal sources is more readily absorbed than non-haem-Fe derived from plant food sources (Beard *et al.* 1996). A practical example was given recently of how the Fe needs of very young children can be met. For the appropriate intake of haem-Fe, the daily consumption required is 'one heaped tablespoon of finely chopped grilled lean beef or lamb, or about 3½–7 heaped tablespoons of skinless, chopped, baked chicken, or about eight heaped tablespoons of steamed, mashed fish fillet' (Mira *et al.* 1996). What proportion of families in developed, and far less in developing populations, could habitually comply?

Iron stores and markers

According to WHO, Fe-deficiency anaemia is present when the haemoglobin (Hb; g/l) concentration in children is < 110, in men < 130, in women < 120, and in pregnant

women < 110 (DeMaeyer *et al.* 1989). However, Hb level is considered by many to be a relatively crude indicator of Fe stores. Of biochemical markers, the most widely used is serum ferritin concentration. The lowest limit of adaptation has been defined as a serum ferritin level of 12 µg/l, below which Fe stores are considered to be fully depleted (Cook *et al.* 1992). Another Fe marker is serum transferrin receptor (Skikne *et al.* 1990; Cooper & Zlotkin, 1996); this marker is less likely to be affected by chronic infection, as is the case with ferritin level; when the receptor level falls below 7.0 mg/l, it is considered that there is a deficit in tissue Fe.

Some examples of levels of serum ferritin are given in Table 2. In an investigation made in the USA, 9% of toddlers aged 1–2 years and 9–11% of adolescent girls and women of child-bearing age were considered to be Fe deficient; of these, Fe-deficiency anaemia was found in 3 and 2–5% respectively (Looker *et al.* 1997). In the UK, in schoolchildren aged 12–14 years, only 1% boys and 4% girls had serum ferritin levels of < 10 µg/l (Nelson *et al.* 1993). In contrast, in a study of Northern Ireland university students, 40% had serum ferritin levels < 10 µg/l; moreover, a further 35% were found to have levels of 10–20 µg/l (Armstrong, 1989). A further puzzling situation was revealed in New Zealand, where a group of vegetarian women in good health had a very low mean ferritin level (13.6 µg/l; Alexander *et al.* 1994); 4.7% were considered to be Fe deficient. Yet, among omnivorous women, despite higher intakes of haem-Fe, the percentage considered deficient was only slightly less (4.2), although they had a higher average ferritin level of 33.6 µg/l.

In less-prosperous and developing populations, WHO considers that, overall, half the children and women and one-quarter of the men are Fe deficient (DeMaeyer *et al.* 1989). However, as with Fe intake, deficiency situations vary enormously. In Mexico, according to one report, 10–70% of the population are Fe deficient, despite the fact that in most studies Fe intake appeared to be greater than that recommended (Rosado *et al.* 1995). In South Africa, in a study of 11-year-old rural African children, the mean serum ferritin level was 37.0 µg/l; none had a level < 12 µg/l. In the group of rural white children studied,

Table 1. Mean daily intakes of iron (mg) in various populations (Mean values and standard deviations)

| Study group | Males | | Females | | Reference |
|---------------------|-------|-----|---------|-----|---------------------------------|
| | Mean | SD | Mean | SD | |
| Whites | | | | | |
| 7–8 years | 9.4 | 3.4 | | | Ruxton & Kirk (1996) |
| 12–14 years | 12.3 | 4.8 | 9.6 | 3.6 | Nelson <i>et al.</i> (1993) |
| 35–49 years | 12.1 | | 8.4 | | Block & Subar (1992) |
| Adults: Omnivores | 17.4 | 6.3 | 13.5 | 2.7 | Alexander <i>et al.</i> (1994) |
| Vegetarians | 20.2 | 5.5 | 15.5 | 3.8 | Alexander <i>et al.</i> (1994) |
| Africans | | | | | |
| 11 years: Rural | 9.0 | 3.7 | | | Lamparelli <i>et al.</i> (1988) |
| Urban | 10.5 | 4.5 | | | Lamparelli <i>et al.</i> (1988) |
| 19–44 years, urban | 10 | 6 | 7 | 4 | Bourne <i>et al.</i> (1993) |
| 25–50 years, rural | 21.4 | 8.7 | 21.6 | 8.1 | Vorster <i>et al.</i> (1994) |
| 60+ years, rural | | | 12.1 | 4.3 | Walker <i>et al.</i> (1992) |
| Indians | | | | | |
| Durban, 18–22 years | 13.1 | 3.6 | 10.6 | 2.6 | Booyens <i>et al.</i> (1969) |

Table 2. Serum ferritin levels ($\mu\text{g/l}$) in various populations

| Study group | Males | Females | Reference |
|----------------------|--------|---------|-------------------------------------|
| Whites | | | |
| 10–11 years | 18.6 | | Van Poppel <i>et al.</i> (1991) |
| 11 years: Rural | 32.3 | | Lamparelli <i>et al.</i> (1988) |
| Urban | 30.3 | | Lamparelli <i>et al.</i> (1988) |
| 12–14 years | 31.4 | 30.4 | Nelson <i>et al.</i> (1993) |
| 14.5–18.4 years | 17.3 | 15.3 | Armstrong (1989) |
| 18–40 years | 73.3 | 34.9 | Weight <i>et al.</i> (1992) |
| Adults: Omnivore | 105.4 | 33.6 | Alexander <i>et al.</i> (1994) |
| Vegetarians | 36.6 | 13.6 | Alexander <i>et al.</i> (1994) |
| Pregnant, 0–3 months | | 27.5 | Guidozzi <i>et al.</i> (1995) |
| Africans | | | |
| 11 years: Rural | 37.0 | | Lamparelli <i>et al.</i> (1988) |
| Urban | 23.7 | | Lamparelli <i>et al.</i> (1988) |
| 17–54 years | 165.0 | 65.1 | PL Jooste (personal communication) |
| 20–55 years | | 164.0 | PL Jooste (personal communication) |
| 15–45 years | | 62.0 | Kuvibidila <i>et al.</i> (1994) |
| 60 years | 312.0* | 151.0* | Johnson & van der Westhuyzen (1990) |

* Median.

mean ferritin level was $32.3 \mu\text{g/l}$; 2.1% had a low ferritin level (Lamparelli *et al.* 1988). In Zaire, in a study of women, mean Hb and serum ferritin levels were 111 g/l and $62 \mu\text{g/l}$ respectively; none had a level of ferritin $< 12 \mu\text{g/l}$ (Kuvibidila *et al.* 1994). In a number of populations in sub-Saharan Africa, often serum ferritin levels are elevated. This is partly because of adventitious uptake from Fe vessels used for food preparation, which can lead to Fe overload (Walker & Arvidsson, 1953), and partly due to infections, particularly from malaria and hookworm, as already mentioned (Fleming, 1989). In elderly rural Africans, the poorest of the poor socio-economically, studies revealed serum ferritin values to be high; the mean was 312 (range 135–355) $\mu\text{g/l}$ in men and 150 (range 9–285) $\mu\text{g/l}$ in women; none of the men but 3% of women were considered to be Fe deficient (Johnson & van der Westhuyzen, 1990). In Cape Town, in a cross-sectional representative sample, in those aged 35–44 years median serum ferritin level was very high (182.3 and $62.1 \mu\text{g/l}$ for men and women respectively; PL Jooste, personal communication).

Of Asian populations, in India in a study of girls aged 11–14 years from a rural area and from urban slums, 25 and 13% respectively had low serum ferritin levels $< 12 \mu\text{g/l}$ (Vasanthi *et al.* 1994). In Indonesia in a group of pregnant women, 49% had a Hb level $< 105 \text{ g/l}$, mean ferritin level was $28.0 \mu\text{g/l}$ and 33.8% had levels $< 20 \mu\text{g/l}$ (Ridwan *et al.* 1996).

There is much that is difficult to explain with regard to serum Fe levels and their significance to health. Moreover, several studies have shown a lack of association between Fe intake and serum ferritin levels (Heitmann *et al.* 1996).

In Africa, since, as indicated, ferritin levels are affected by infection and by Fe overload, it is probable that the level of serum transferrin receptor will be a more reliable measure of Fe status; however, relevant studies are few. In Nigeria, severe malnutrition in young children was found to be associated with decreased levels of this component (Akenami *et al.* 1997). It is interesting that the mean level

in the control group was higher than that reported in Finnish children (Kivivuori *et al.* 1993); the African group was regarded as having adequate Fe status.

Iron-deficiency stigmata

Infants and children and lower cognitive ability

At an International Conference, held in 1988, on Iron Deficiency and Behavioral Development, most of the studies presented indicated significant differences in behaviour between anaemic and non-anaemic groups of young and of older children. It was concluded that 'iron deficiency should be prevented and treated in all children' (Haas & Fairchild, 1989).

Regarding individual investigations, in the often-quoted study of a group of Costa Rican children aged 5 years, those who had Fe-deficiency anaemia in infancy were considered to be at risk of long-lasting developmental disadvantage as compared with their peers with better Fe status (Lozoff *et al.* 1991). With respect to the magnitude of the differences, the mean adjusted Woodcock–Johnson preschool cluster score (Woodcock, 1982; a test score for spatial relations and visual audio-learning) for the children who had moderate anaemia in infancy ($n 30$) was 448.6 (SD 9.7), as compared with 452.9 (SD 9.2) for the rest of the children ($n 133$; $P < 0.01$; a difference of 1%). The visual motor integration score averaged 5.9 (SD 2.1), as compared with 6.7 (SD 2.3; $P < 0.05$; a difference of 13%). Differences of this order of magnitude between anaemic and non-anaemic groups of preschool children have been reported for a number of other groups (Pollitt, 1993), e.g. those studied in India (Seshadri & Gopaldas, 1989). In Indonesia, in a meticulously undertaken double-blind cross-over study, fifty Fe-deficient anaemic West Javanese schoolchildren scored averages of 88.5 and 88.8 respectively for their motor and mental skills, compared with 105.3 and 105.4 for forty-seven children with normal Fe levels in their blood. After receiving 3 mg Fe/kg daily for 4

months the scores for the Fe-deficient anaemic group increased to 112.0 and 108.1 respectively (Idjaradinata & Pollitt, 1993). These gains (20–22%) and those noted previously certainly are significant and, potentially, could be important for the economy of the country.

In Western populations, corresponding studies on children, rich and poor, appear to be limited. In Birmingham, UK, a series of toddlers aged 17–19 months with Hb levels of 80–110 g/l received an Fe supplement for 2 months. This treatment resulted in an increased rate of weight gain and, moreover, more of them achieved the expected rate of psychomotor development (Auckett *et al.* 1986). Notwithstanding, the authors concluded that it was unlikely that Fe-deficiency was the only culprit in the slower development of the underprivileged children. In this connection, account must be taken of a report from Indonesia, in which it was reported that the Fe supplementation of Fe-replete children may retard their growth (Idjaradinata *et al.* 1994). In an investigation done in London, on a group of young adults (average age 20 years), to determine whether low Fe status influences psychological functioning, it was found that 3.8% of males and 31.8% of females had ferritin levels < 12 µg/l (Fordy & Benton, 1994). However, from the five tests of cognitive function administered, there were no significant differences between the anaemic and non-anaemic groups. It was considered that the presence of ferritin levels below the accepted normal range provided little grounds for concern. In the USA, in Baltimore, a randomized study was undertaken of the cognitive effects of Fe supplementation in non-anaemic Fe-deficient adolescent girls (Bruner *et al.* 1996). The serum ferritin level averaged 9.1 µg/l (in the control group, it was 8.5 µg/l). Although tests for memory improved slightly, but significantly ($P < 0.02$), those for energy, mood and concentration were unaffected. One conclusion reached was that 'there is only weak evidence of relationships between dietary status and cognitive function, and none of which relate directly to iron in spite of the fact that iron deficiency is the most common deficiency in the UK' (Nelson, 1996).

In brief, in the numerous investigations pursued on poorly-circumstanced children, when given Fe supplements the cognitive scores of the deficient groups rose significantly. The differences between the supplemented and non-supplemented groups were slight in some studies, but were very marked in others.

Children: physical ability and capacity

In The Gambia, in Africa, a group of boys and girls aged 11–14.5 years who received a multi-vitamin and an Fe supplement for periods of 5 and 10 weeks were subjected to various tests (Powers *et al.* 1987). No significant changes were observed with respect to O₂ consumption and heart rate. In a particular subgroup which initially had poor vitamin or Fe status, there was a significantly lower score in the workload test in the non-supplemented group, i.e. a decrease from 21.0 (SD 0.80) to 20.8 (SD 0.59) kJ/min ($P < 0.05$), a difference of 1%. A further study made on children in The Gambia, which was also concerned with the

effects of intakes of vitamins and of Fe on physical ability, revealed that supplementation with riboflavin, thiamin, vitamin C, and Fe, together, had the effect of raising treadmill work performance significantly (Powers *et al.* 1988). However, no significant benefit was evident when supplementing with either riboflavin and vitamin A together, or with Fe alone. It was noted, and this concerns a phenomenon insufficiently appreciated, that in the tropical context described, the use of micronutrient supplements could increase susceptibility to malaria. The conclusion reached was that the investigations carried out raised as many questions as they resolved.

In studies done in South Africa on a group of African schoolchildren, it was reported that mean values for O₂ consumption, as determined from performance in the 12 min walk-run, were closely similar to those reported for white children (Walker *et al.* 1972). In the latter study, it was also found, although not reported, that pupils in lower and upper quartiles of performance did not differ significantly in their mean Hb levels (127 (SD 12) and 129 (SD 13) g/l respectively; $P < 0.05$). In relation to everyday physical activity, a large proportion of rural African schoolchildren walk many miles daily to attend school (Walker *et al.* 1993).

In Canada, in 1972, 12-year-old Inuit boys of the same weight but slightly lower height than English Canadian boys, were found to have far higher mean O₂ consumption levels (70 v. 56 ml/kg per min) for reasons not explained (Shephard, 1991).

Clearly, many factors, in addition to the level of Fe stores, influence physical ability.

Adults: working capacity

In developing populations, early studies undertaken in Guatemala indicated a linear relationship between Hb level and Harvard Step Test performance (Viteri & Torun, 1974). Fe supplementation studies carried out on rubber tappers in Indonesia (Basta *et al.* 1979) and on tea pickers in Sri Lanka (Bradley *et al.* 1988) noted significant gains in productivity after the treatment of those individuals with significant anaemia. In the case of the tea pickers, it was considered that since the average reduction in productivity due to anaemia was about 20%, the disadvantage could prejudice economic output very significantly. In an investigation made on cotton-mill workers in Beijing, China, Fe supplementation in a group who had Fe-deficiency anaemia revealed that a rise of 10 g/l in Hb level was associated with an improvement in production efficiency of 14% (Li *et al.* 1994). In Jakarta, Indonesia, at a jute factory, workers with anaemia (Hb < 120 g/l) produced an average of 5.3% less in the factory and performed an average of 6.5 h less housework per week (Scholz *et al.* 1997). These observations are in agreement with an investigation made in the UK. In a group of 11–14-year-old schoolgirls, largely white and Indian in ethnic origin, it was found that in step test performance, for a given body size, the O₂ capacity of the blood was lower in those with Hb levels ≤ 120 g/l ($P \leq 0.04$; Nelson *et al.* 1994). As already mentioned, the gains described could

have a significant bearing on the agricultural and industrial economies of the countries.

Pre-term birth and low birth weight

It has been claimed that severe anaemia is responsible for up to 40% of the half million deaths associated with childbirth each year (Seymour, 1996).

First, in relation to women of lower socio-economic status, in a group of poor pregnant women studied in New York, Fe-deficiency anaemia was found to be associated with a higher risk of preterm delivery and lower birth weight (Allen, 1993). However, three-quarters of the pregnant women diagnosed with anaemia were not Fe deficient. The actual prevalence of Fe-deficiency anaemia (serum ferritin < 12 µg/l) was very low (3.5%); it explained only 5.5% of the risk of preterm birth.

In an inner-city population in Camden, New Jersey, the risk of preterm birth attributed to Fe-deficiency anaemia was reported to amount to 5.5% overall; 11.1% in the case of African-Americans (Scholl *et al.* 1992). These results were considered to reflect the low prevalence of Fe-deficiency anaemia for the entire cohort. It was concluded that Fe-deficiency anaemia made only a modest contribution to the aetiology of preterm delivery in the group of poor urban women studied. In another study relating to disadvantage in the anaemic group, 12.7% had previous low birth weight, 15.2% had previous preterm birth and 9.8% were in the non-anaemia group (Scholl & Hediger, 1994). The view was expressed that only women who are frankly anaemic, with an Hb level of ≤ 95 –100 g/l, require supplementation.

In developing populations, as in Africa, in areas where malaria and hookworm are widespread, additional Fe has been shown to benefit the outcome of pregnancy (Fleming, 1989). At the extreme of severity, with packed cell volume ≤ 0.13 , it was stated that over half the women with heart failure die. However, it is noteworthy that in surveys conducted in India and Indonesia, before and after the introduction of an Fe supplemental programme, the prevalence of maternal anaemia still persisted at high levels ($\geq 80\%$ in India and $\geq 60\%$ in Indonesia; Yip, 1996). This level of response is unfortunate, for as Yip (1996) states, it is 'the effect of the actual program operation of iron supplementation through the primary health care system which is a true measurement of effectiveness, which reflects the impact under real world conditions'.

Numerous examinations of evidence and the conclusions reached have been assessed by reviewers and authoritative bodies. An examination of the results of seventeen controlled clinical trials revealed no significant benefit to patients given prophylactic Fe and vitamin supplements during pregnancy (Hemminki & Starfield, 1978). The variables studied included birth weight, length of gestation, infant morbidity and mortality, and maternal morbidity and mortality. A similar conclusion was reached, as indicated in the background articles, by the US Public Health Service Expert Committee Panel on the content of prenatal care (Blankson, 1990). In a review on pregnancy in Western

women, it was considered that it was uncertain whether Fe and vitamin supplements exert a beneficial effect on length of gestation, birth weight, or on infant and maternal mortality or morbidity (Williams & Wheby, 1992). A policy statement of the US Preventive Services Task Force (1993), reported, 'There is currently little evidence from published clinical research to suggest that routine iron supplementation during pregnancy is beneficial in improving clinical outcomes for the mother, fetus, or newborn. The evidence is insufficient to recommend for or against routine iron supplementation during pregnancy. Although observational data suggest that pregnant women with anaemia (haemoglobin level less than 100 g/l) are at increased risk of pre-term birth, low birth weight, and other adverse outcomes, it is unclear from such evidence whether anaemia is responsible for these outcomes and whether they can be prevented through iron supplementation. Similarly, it is unclear whether iron supplementation during pregnancy can reduce the incidence of iron deficiency in infants, a condition that has been associated with delayed psychomotor development.' In Finland, the conclusion was reached that for pregnant women in everyday good health, routine Fe prophylaxis is unnecessary (Hemminki & Meriläinen, 1995).

A recent study on 153 602 pregnancies in inter-ethnic women in the north-west Thames region of the UK concluded that 'haemoglobin concentrations < 95 g/l seem to be remarkably harmless' (Steer *et al.* 1995). Although, in that region, low Hb concentrations were found to be more common in some ethnic minorities, notably Africans, Afro-Caribbeans, and Indo-Pakistanis, it was concluded this does not account for the increase in low birth weight and preterm labour in these groups, which persists at all Hb concentrations. 'It may be that haemoglobin concentrations, birth weight, and length of gestation are genetically programmed to be different in these groups and are therefore physiological.' (Steer *et al.* 1995). A number of authors have drawn attention to dangers in the provision of unselected Fe medication for all pregnant women (Klebanoff *et al.* 1991; Hollan, 1996).

In brief, in the large majority of contexts described, Fe supplementation in pregnancy appears unwarranted.

How applicable are the results of clinical trials to public health programmes?

Recently it has been emphasized that clinical trials have their limitations, and that 'only a solid examination of the laboratory and epidemiological evidence can approximate the answers to most questions of interest' (Block, 1995). It has also been cautioned that randomized trials in many areas of health care have low external validity (Black, 1996). Furthermore, in relation to this issue, the pertinent question has been raised, 'Why is there a discrepancy between the impact of iron supplementation observed in properly conducted clinical trials and that observed in large-scale public programs?' (Yip, 1996).

First, in the investigations described on the cognitive capacity of schoolchildren it is important to know: how did the individuals, with and without Fe-deficiency anaemia,

fare in their general school examinations, both termly and annually (Ashby, 1996)? Ultimately, it is the results of such examinations which largely determine the child's future, e.g. whether he (she) attends university or not. Would the differences detected in clinical trials be manifest quantitatively, or would the differences be lessened, or even not evident, due to the operation of numerous other influential factors, dietary and non-dietary? In relation to pupils with unsatisfactory Fe status, there is a further question: would the differences in the test scores have a bearing on the nature of their future occupations? In some reviews it has been concluded that no information implicates academic or social handicaps in adults who experienced Fe deficiency during childhood or the later years (Cook & Lynch, 1986; Kretchmer *et al.* 1996). Clarification of this issue will require the undertaking of cohort and other studies.

In respect of other influencing factors, it has been stressed that 'the influence of microenvironmental, socio-economic, and parenting behaviors on cognitive development in young children may well be more powerful influences than iron status *per se*; the effect of iron deficiency needs to be considered as only part of the framework of events that determine cognition and psychomotor development' (Beard, 1995). Regarding lack of specificity, in a recent study in Costa Rica it was concluded that since lower mental test scores persisted in infants with Fe-deficiency anaemia despite extended oral Fe therapy and an excellent haematological response, Fe-deficiency anaemia may serve rather as a marker for a variety of nutritional and family disadvantages that may adversely affect infant development (Lozoff *et al.* 1996). Others have emphasized the need for more research (Pollitt, 1997).

Turning to work performance, with adults and with children, many factors (dietary and non-dietary) are likely to be influential. In the various work production situations investigated, it is necessary to know the magnitude of the increased production over a period of, for example, 1 year in a supplemented compared with an otherwise un-supplemented plantation or industrial labour force. It would be important also to know, in a given large work force divided into grades of excellent *v.* poor performers, to what extent such gradings correlated with Fe status. Additionally, it could be asked to what extent would the disadvantage from Fe deficiency be detectable in developing populations with lower intensities of physical activity, as largely prevails in Africa, especially in the increasing urban populations. Only through enquiries of the type described can the extent of the drawbacks of lower physical ability associated with Fe deficiency be estimated, and of its bearing on community, regional or national economies.

Regarding the outcome of pregnancy, in relation to preterm birth and low birth weight, the following view has been expressed, 'It is encouraging that there is clear evidence that iron supplementation is efficacious under careful clinical trials; however, the review by the Mother-Care Project raised the concern that there is no good evidence that iron supplementation is effective when implemented as a large-scale program through the primary health care system. Proper evaluation of the effectiveness of iron supplementation on a national basis under program conditions is difficult to conduct, and data are not

available.' (Yip, 1994). As to other suggestions made in this field, it has been urged that longitudinal measurements of Fe status should be made to determine the stages of pregnancy during which Fe-deficiency anaemia predicts poor pregnancy outcome (Allen, 1997).

There is certainly no desire to minimize the adverse role of Fe deficiency under particular conditions, as in contexts in Africa and India where, for example, infections may be severe. Furthermore, evidence in the various fields discussed has not been examined exhaustively. With respect to Western populations the impression emerging is that, apart from extremes, assurance is lacking that the differences in performance between Fe-deficient and non-Fe-deficient groups in the variables discussed, as revealed by clinical trials, have resulted in corresponding detectable benefits in respect of well-being, morbidity and mortality. In developing populations, disadvantages arising from Fe deficiency are likely to be more potent; but even in this respect, it would seem that in general authors now regard these as of limited clinical concern. In *Tropical Pathology*, in a long and detailed review on anaemia, the adverse sequelae were not granted a reference (Knox-Macaulay, 1995). In the newly-published *Manson's Tropical Diseases*, only two references are given (Fleming, 1996).

Conclusion

For large proportions of populations, especially in the Third World, Fe intake is less than the amounts recommended. Serum ferritin levels and other haematological indices indicate that large proportions, albeit minorities, have low stores of the element. However, in each of the areas of Fe deficiency discussed, it is apparent that there are uncertainties over the validity of Fe needs and subsequent benefits from supplementation. The crucial problem concerns the insufficiency of information on the translation of the results of clinical trials to the conditions of everyday life, i.e. 'the real impact of interventions on 'at risk' segments of populations' (Beard, 1996). Currently, in developed countries (Dean, 1995; Awuonda, 1996), and much more so in generally impoverished developing countries (Gilks & Haran, 1995; Amanor-Wilks, 1996), financial resources for public health are limited. On this account, it cannot be held that the remedying of Fe deficiency has a high priority in comparison with other more cost-effective health needs, both dietary (as in the remedying of severe protein-energy malnutrition in the very young) and non-dietary (as in the provision of water supplies and the availability of 24 h clinics).

While general Fe supplementation in certain populations, especially in particular regions, is recommended, more information is needed not only of the extent of the advantages but also of possible disadvantages in Fe-replete subjects, i.e. in the majorities of populations, both developed and developing. A recent caution in this respect (regarding 'what harm can it do?'), concerns the recommended widespread practice of increasing the intake of another element (Ca) by supplementation, in endeavours to maintain bone mass at its maximum to avoid hip fracture. In the USA, it has now been shown that the quartile of

women with the highest bone mass, compared with those with the lowest bone mass, is at 3.5 times greater risk of developing breast cancer (Zhang *et al.* 1997).

In developing populations, none would doubt the need for supplementation in particular populations and regions, e.g. where malaria is common. However, even in this context, the results of some trials in which efforts were made to remedy Fe deficiency have been disappointing (Ekjidokun *et al.* 1996; Nakazawa *et al.* 1996).

For very young children, it has been recommended that lean meat or fish should be introduced at 6–9 months to supply 0.71 mg/d haem-Fe (Mira *et al.* 1996), Fe from plant sources being less bioavailable. However, meat and fish in the amounts recommended are relatively inaccessible to those whose need is greatest. While a food-based approach is the best way forward, it can only happen as poverty is lessened. Diets will then become more varied and nutrients more available, and there will be less sickness and ill-health, which have a negative effect on Fe status as people rise in socio-economic status.

In some groups of less-privileged populations, in which it would be desirable to increase Fe intakes by supplementation, there is now evidence that the cost can be reduced by providing equally effective weekly instead of daily pills (Galloway & McGuire, 1996; Berger *et al.* 1997).

As to food fortification, in the British Columbia Native Reserve, Canada, the incidence of anaemia in infants has been reduced from more than 50% to less than 5% due to the provision of an Fe-fortified formula (Quinn, 1996). In a recent survey in Venezuela, in Caracas, the overall prevalence of low serum ferritin in schoolchildren was 36.6%, and that of anaemia was 19%. Within 2 years of the introduction of fortified wheat flour and fortified precooked maize the prevalence of low serum ferritin decreased to 15.8% and that of anaemia due to Fe deficiency fell to 6.8% (Layrisse *et al.* 1996). It was estimated that there was a mean average increase in Fe intake of 6 mg/d from fortification with ferrous fumarate. Although this amount is lower than the 10 mg/d increase reported in Thailand (Garby & Areekul, 1974), it is nearly double the amount of additional Fe obtained elsewhere in Latin America using NaFe-EDTA (Viteri *et al.* 1983), and approximately equal to the level of fortification practiced in South Africa using curry powder fortified with NaFe-EDTA (Ballot *et al.* 1989).

Apart from food fortification, increased dietary intakes of Fe should be encouraged, despite the general indifference of the general public to measures for health improvements (Austoker, 1995). It is gratifying that there are now new worldwide initiatives through WHO to make guidelines more positive, practical and understandable and, therefore, more sustainable for the general public (Joint FAO/WHO Consultation Committee, 1996). The move is towards food-based dietary guidelines, which should be designed for particular populations and based on existing eating patterns. While there is little likelihood of public indifference being translated into public eagerness, it could be that responses and results even from a minute proportion of the population would encourage others to raise not only their intake of Fe, but possibly more importantly, that of other micronutrients.

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