Strategies to control nutritional anemia\textsuperscript{1,2} 

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Nutritional iron deficiency is the most common deficiency disorder in the world, affecting more than one billion people. Two-thirds of children and of women of childbearing age in most developing nations are estimated to suffer from iron deficiency; one-third of them have the more severe form of the disorder, anemia. Furthermore, unlike many nutritional diseases, such as vitamin A deficiency, which can lead to blindness, and iodine deficiency, which can cause retardation and deafness, iron deficiency is found in all societies, developing and industrialized alike. In the United States, Japan, and Europe, for instance, between 10\% and 20\% of women of childbearing age are anemic (1, 2).

Iron deficiency commonly remains unrecognized. Because of subtle symptoms, such as pallor, listlessness, and fatigue, the disorder is not regarded as life-threatening. Yet iron deficiency can have a multitude of effects and can even cause death. The main function of iron in the body is in erythropoiesis; thus, many of the problems of iron deficiency arise from anemia. Others are related to the shortage of iron in tissues, and sometimes to a combination of both. Thus, iron deficiency severe enough to produce anemia is associated with a substantial reduction in work capacity; impaired behavior and intellectual performance; impaired capacity to maintain body temperature in a cold environment; increased risk of lead poisoning, particularly in young children; and decreased resistance to infection. In fact, cell-mediated immunity is often found to be impaired before anemia can be detected and before overt clinical signs are observed (3). Because of the magnitude and consequences of the problem of nutritional anemia in the world, governments of the world committed themselves at the International Conference on Nutrition in Rome in December 1992 to reduce by the year 2000 the prevalence of iron deficiency in women of childbearing age by one-third compared with the levels in 1990 (4). For deficiencies of the other two micronutrients, vitamin A and iodine, the goal set was virtual elimination by the year 2000. This indicates the intractable nature of nutritional anemia.

Basically, four approaches can be used to combat malnutrition of the three micronutrients: supplementation, fortification, dietary diversification, and public health measures (3). Problems of both efficacy and effectiveness reduce the success of programs to combat micronutrient malnutrition, including nutritional anemia (3). Efficacy can be defined as the relative success in achieving the desired goal under ideal conditions whereas effectiveness is the relative success also taking into account the ability to intervene. Four factors in particular are important in determining efficacy of nutritional anemia control programs: bioavailability of iron, availability of other nutrients that may affect hematopoiesis, increased red cell loss and destruction, and the anemia of inflammation. In addition, possible side effects of the programs need to be considered. These factors will be considered in turn.

Factors influencing iron bioavailability have been studied in great detail and an algorithm was developed for its prediction (5). Because this algorithm does not take into account all of the factors associated with iron bioavailability, it has been proposed that a new algorithm be developed based on the mnemonic SLAMANGHI (6). The nine factors to be considered are as follows: species of iron compound, molecular linkage, amount of nutrient consumed in a meal, matrix in which the nutrient is incorporated, absorption modifiers, nutrient status of the host, genetic factors, other host-related factors, and interactions. Perhaps the most important factor in determining iron bioavailability, especially when dietary modification is considered, is the balance between the intake of nonheme iron and that of absorption modifiers, particularly vitamin C, phytic acid, and tannins.

Other nutrients for which availability may affect erythropoiesis include folic acid, vitamin B-12, riboflavin, and vitamin A. The factor that has received the most attention in recent years is probably vitamin A because of the finding that supplementation with vitamin A increases hemoglobin concentrations in anemic women with marginal or just adequate vitamin A status (7), probably as a result of an effect on the uptake of iron by the erythropoietic system (6).

Increased red cell loss and destruction can be due to heavy menstrual losses, blood loss into the gastrointestinal tract resulting from damage by parasites such as hookworm and by intestinal disease such as cancer, and red cell destruction as a result of hemoglobinopathies and parasitic blood diseases, particularly malaria. The anemia of inflammation is poorly understood but may be related to interference of transferrin iron uptake by hematopoietic cells produced by the acute-phase protein α\textsubscript{1}-antitrypsin (8), which in turn is stimulated by the inflammatory cytokines (9).

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There are several side effects of increased iron supply that need to be assessed in relation to the positive effects that can be achieved. In this regard, the most important is iron overload, thus making it necessary for those implementing iron-deficiency control programs to take steps to identify people in the population with a propensity for iron overload (10). In addition, the negative effects of increased iron supply on the body's host defense system need to be balanced against the positive effects in general mentioned above and in particular with respect to host defense. These include the direct prooxidative effects of iron, effects of iron on acute-phase protein concentrations in serum, and cell-mediated and humoral immunity. These effects are mediated to a large extent by cytokines (9).

The paper by Northrop-Clewes et al (11) in this issue of the journal makes the important point that iron supplementation should be accompanied by improvement of vitamin A status. This conclusion is based on a significant increase in α1-antichymotrypsin concentrations in serum in iron-supplemented infants, which is counteracted to some extent in those infants whose serum retinol concentrations increased over the period of the intervention. However, the statistical analysis would have preferably involved analysis of variance after transformation of data or multiple regression with iron intervention as a dummy variable. Also, the significance of effects were derived from a cross-sectional analysis of postintervention values instead of the usual comparison of between-group differences of the changes over the intervention period. With the method used, differences at baseline, although they may not be significant, can lead to incorrect conclusions. Additionally, differences between groups were tested with nonparametric statistics whereas regression analyses were carried out with parametric statistics.

Placing the findings of Northrop-Clewes et al in a broader context of efficacy, there is evidence that vitamin A stimulates erythropoiesis and reduces the anemia of inflammation but possibly does not affect iron bioavailability or red cell loss and destruction. The suggestion that the lack of effect of carotenes in dark-green leafy vegetables in increasing serum and milk retinol concentrations was due to the already high intake of vegetables as indicated by high serum lutein concentrations is contrary to the results of de Pee et al (12). The view of Northrop-Clewes et al that any β-carotene absorbed would be converted immediately to retinol does not explain the ready conversion of β-carotene present in the wafer used in the studies of de Pee et al to retinol. As far as the postulated negative effects of iron are concerned, is there any evidence of oxidative damage or is the overall balance of nonspecific and acquired immune system compromised by giving iron alone? In many ways, the paper by Northrop-Clewes et al raises many questions that should be addressed in well-designed studies and reported in papers that place the work in context.

REFERENCES

7. Subarno D, West CE, Muhial, Karyadi D, Hautvast JGAJ. Not only supplementation with iron but also with vitamin A is necessary to combat nutritional anaemia in pregnant women in West Java, Indonesia. Lancet 1993;342:1325–8.