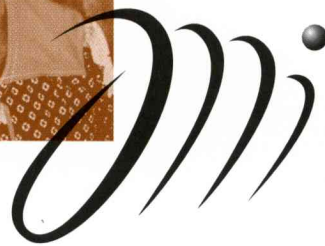# Major Issues in the Control of Iron Deficiency
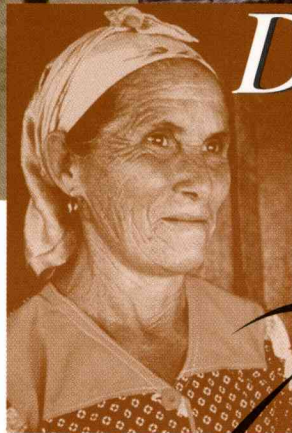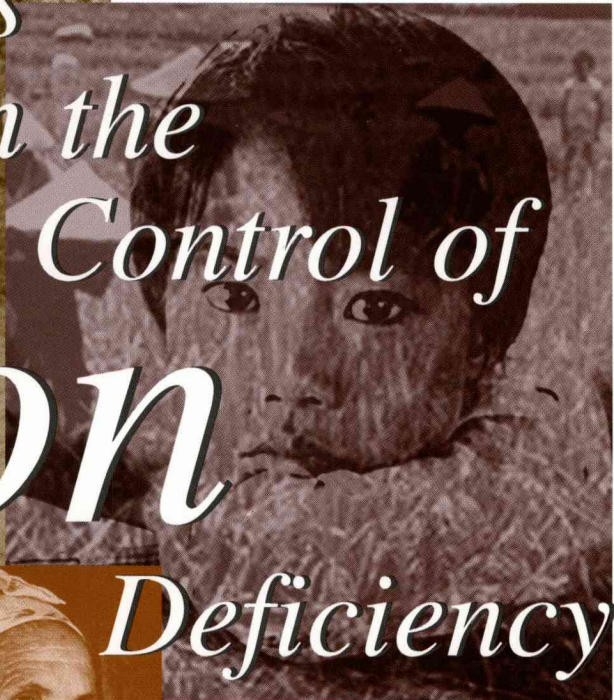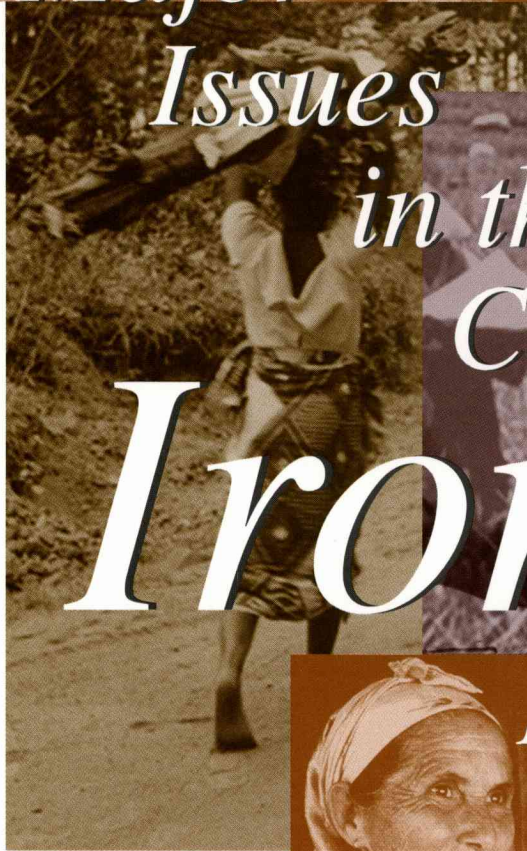
The Micronutrient Initiative

Major Issues

in the

Control of Iron Deficiency

Stuart Gillespie

The
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CONTENTS

FOREWORD

Iron-deficiency anemia (IDA) is a public-health problem of staggering proportions. It affects not tens of millions but hundreds of millions of people around the world, most of them women and children. It impedes the physical and cognitive development of young children and their ability to resist illness. It keeps older children from performing well and, in some cases, staying in school. Anemia, largely caused by iron and folate deficiency, is estimated to contribute to one in five maternal deaths. The high rates of iron-deficiency anemia globally constitute a public-health emergency as compelling and harmful as epidemics of infectious diseases.

In the last decade, reducing micronutrient deficiencies, especially iodine and vitamin A deficiency, has been achieved through nation-wide programs in developing countries, thanks to the work of governments, donors, and other partners who have supported advocacy and technical assistance. Salt iodization and the widespread adoption of large-scale vitamin A supplementation, for instance, are striking global success stories. The control of iron-deficiency anemia, however, continues to lag behind, notwithstanding the fact that it is the most prevalent nutritional deficiency in the world.

As with vitamin A, combatting anemia is probably best understood in most countries as requiring a combination of approaches. National programs that include food fortification, iron supplementation for certain well-defined groups, nutrition education, promotion of exclusive breastfeeding for up to 6 months, and social marketing for improved available iron in the diet — through increasing dietary enhancers and minimizing the effect of iron inhibitors — may all be part of the solution.

In addition, anemia is perhaps more complicated than iodine and vitamin A deficiencies because it is only partly caused by dietary insufficiency of nutrients. Dietary insufficiency or inadequate bioavailability of iron, folate, and other nutrients contribute significantly to anemia but, in many countries, malarial and helminth infections and AIDS (acquired immune deficiency syndrome) are also important causes of anemia. In these cases, food-based interventions alone will be insufficient. The challenge then is to develop policy based on knowledge of multiple etiologies of anemia, and to mobilize support for efficacious and effective interventions.

Although information on the problem and its treatment is widely available, this knowledge has not been synthesized in a form that is easily assimilable and applied. There is also a need to pro-actively address key issues related to effective programming and to facilitate the development of an expert consensus on optimal solutions based on the best scientific knowledge and experience.

This book has been compiled by the Micronutrient Initiative and the United Nations Children's Fund (UNICEF) with the objective of synthesizing the various anemia-control strategy components that clearly need to fit together. We hope that it will be useful to policymakers and program managers alike in planning and implementing programs that make significant inroads to alleviate anemia by the end of this decade.

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PREFACE AND ACKNOWLEDGMENTS

Very high prevalence of iron deficiency, and its severe form anemia, has detrimental consequences for health and well-being. The decision made by almost all governments in early 1990's to give priority attention to reducing this condition created an increasingly intensified need for effective control programs against iron deficiency and anemia. To bring together updated information and field experiences in dealing with the problem, and to highlight the major constraints for effectiveness of implemented programs, the Micronutrient Initiative commissioned the preparation of this background paper with the aim of representing international views and as far as possible the consensus among the experts on the major relevant issues. The aim was to define the problem and interventions to deal with the iron deficiency and anaemia, to examine various control strategies for effectiveness and to suggest ways to increase their impact in large scale and national programmes. Main issues were summarized for the easy reference in Annex I. In response to the concerns expressed by some, UNICEF commissioned examination of the practical significance of iron overload for iron deficiency control programmes and particularly the impact of iron fortification of foods in susceptible populations. This section is included in the document as Annex 2.

This document is written by Stuart Gillespie in collaboration with many dedicated individuals expert in this field. The MI requested the reviews from a large number of people with scientific and practical experience in dealing with problem and consequences of iron deficiency and anaemia, and they all generously gave their time and lent their technical expertise for preparation of this document. The Micronutrient Initiative is particularly grateful for constructive detailed comments received from George Beaton, Rebecca Stoltzfus, Ray Yip, Donald Bundy, Thomas Bothwell and Alan Fleming. We sincerely acknowledge valuable comments on draft paper received from E.L. Acadi, David Alnwick, John Beard, Bill Clay, Hernan Delgado, Suzanne Fairweather-Tait, Suzanne Filteau, R. Florinto, Gary Gleason, Leif Hallbery, Jessica Jitta, Janice Johnston, Penny Nestel, the Partnership for Child Development, Sonya Rabeneck, Werner Schultink, Nevin Scrimshaw, Subadra Seshadri, Barbara Underwood, Anna Verster, Sheila Vir, Fernando Viteri, Pattanee Winichagoon, and Stanley Zlotkin.

All stages of planning, preparation and production of this document were coordinated and overseen by Mahshid Lotfi, MI. The MI acknowledges with thanks the help given by Alison Ball and Susan Hodges of International Development Research Centre (IDRC), in literature searches; Tanya Guay, MI, for handling the printing arrangements; and Carrie Smith, MI, who gave administrative assistance in preparation of this publication. The efforts of Gil Croom in copy editing and layout, and of Rosemary Salter in cover design are greatly appreciated.

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INTRODUCTION

INTRODUCTION

Iron deficiency is the most common nutritional disorder in the developing world (ACC/SCN 1991) and the most common cause of nutritional anemia in young children and women of reproductive age. It is estimated that 2,150 million people are iron deficient and 1,200 million of them are anemic (WHO 1991). The economic and social consequences of iron-deficiency anemia, although unquantified, are thought to be enormous and include a significant drain on health-care and education resources and on work capacity as a result of the heightened mortality and morbidity risk of infants and mothers and the reduced physical and mental capacity of large segments of the population.

Of the three micronutrient deficiencies traditionally seen as deserving priority attention — vitamin A, iodine, and iron — iron has in the past tended to suffer relative neglect. In the last decade or so, whether actively or passively, the prevention and control of iron deficiency was to some extent "put on hold" by governments, international agencies, and much of the donor community. Unlike vitamin A and iodine, a mid-decade goal for iron-deficiency anemia reduction was not set in 1993 at the Joint Committee on Health Policy of the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). At the same time, new breakthroughs in our understanding of the consequences of vitamin A deficiency along with the clear feasibility of salt iodization raised the priority attached to these two micronutrients. Indeed, some documents advocated an initial focus on "easier" micronutrients such as iodine (WHO 1991) with a view to demonstrating success more quickly and, hopefully, thus later benefitting other micronutrient programs.

In 1991, a rapid global survey was carried out by WHO to determine where countries stood with respect to situation analyses, planning, and implementation of actions and monitoring and evaluation for the three major micronutrient deficiencies (WHO 1991). For anemia, the vast majority of countries fell into categories of "partial" or "inadequate" for such activities. Only in the Americas and a few Western Pacific countries were comprehensive programs underway. When viewed against the regional figures for anemia prevalence (see *Prevalence*, page 9), a clear imbalance can be seen between the existence of large-scale programs and the need for them — related to intercountry differences in human, economic, and organizational resource configurations and the priority attached to iron-deficiency control.

Iron deficiency and even anemia are often not clearly visible to decision-makers. Despite serious functional consequences, there are no obvious physical manifestations that could serve to galvanize political will. In health-resource allocation, where mortality remains the primary outcome of concern, knowledge of the links of anemia to heightened mortality risk are yet to be internalized by planners. In fact, much of the significant amount of research carried out on the nature and consequences of iron deficiency and anemia remains to be fully communicated, and acted upon, by many policy-makers in countries where the problem is significant. Moreover, there remains a prevalent view that the problem is being taken care of by iron supplements, which are perceived as being available through primary health-care outlets in most countries, and then acquired and consumed by those who needed them. A paucity of data on both process and outcomes leaves this view unchallenged.

There are strong signs that this situation is now changing. Reduction of iron-deficiency anemia is an end-of-decade goal to which various national plans of action for nutrition have been committed, for example, those emerging from the International Conference on Nutrition held in 1992. Better understanding of the deleterious consequences of iron-deficiency anemia and more data showing its persistently high prevalences in many countries are now leading to more concerted action. Although the economic costs of anemia have been known for some time, recent knowledge of the potentially irreversible damage to a child's mental development that anemia can cause early in life is further catalyzing this change. There is a growing recognition that there will be no panacea, rather that a mix of approaches with different time horizons is needed that tackle the various facets of the problem in a complementary and sustainable fashion.

Now also there is a more widespread consensus that more than three micronutrients are of nutritional importance, and complementarities need to be exploited between different approaches to more efficiently combat a range of micronutrient deficiencies. Vertical, self-standing interventions to tackle individual deficiencies do not usually make sense in isolation where, first, it is the same people (usually the poor) who suffer from a cluster of deficiencies and, second, similar remedial approaches (for example, dietary modification and fortification) would be indicated in most cases. For example, social marketing to improve micronutrient-rich foods should consider the fact that a high proportion of the target population may simultaneously be deficient in several nutrients. Approaches need to be integrated, complementary, and as community-based as possible.

The objectives of this overview are:
- To summarize currently available knowledge regarding the prevalence, causes, and consequences of iron deficiency;
- To describe the main strategies to prevent and control iron deficiency;
- To identify the major current issues and constraints to the successful implementation of the various strategies, and make recommendations on how can these be eliminated or minimized; and
- To outline programming steps to be followed in the assessment and analysis of iron deficiency and the design and implementation of effective actions for its prevention and control.

The overview is divided into three main parts. In the first — assessment and analysis — the nature of iron deficiency and iron-deficiency anemia; how it can be assessed; its prevalence, causes, and consequences; and the human requirements for iron at different stages of the life cycle are all described. In the second part, the four major strategies for preventing and controlling iron

deficiency — pharmaceutical supplementation, dietary modification, fortification, and parasitic disease control — are reviewed. For each approach, the major issues and constraints that have emerged from worldwide programmatic experience are discussed. Finally, in the summary and conclusions, guidelines for large-scale program development are summarized and some conclusions are presented. A checklist summary of the main issues identified in the overview is provided in Annex I and a "stand-alone" paper on the practical significance of iron overload for iron-deficiency control programs (with particular relevance to fortification) is provided in Annex II.[1]

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[1] This overview seeks to build on previous reviews and syntheses including WHO/UNICEF/UNU (1996), Yip (1994, 1996a, b, c), Nestel (1995), World Bank (1994), and Gillespie et al. (1991).

Relevant workshops during the 1990s include the United States Agency for International Development/ Opportunities for Micronutrient Interventions (USAID/OMNI) and Partnership for Child Development (PCD) consultative meeting on iron deficiency and cognitive development in September 1996; the USAID/OMNI and UNICEF consultative meeting on iron/multinutrient supplements for children in August 1996; the USAID/OMNI workshop on micronutrient interactions in July 1996; the Ottawa forum on food fortification organized by the Micronutrient Initiative (MI), The Keystone Center, and Program Against Micronutrient Malnutrition (PAMM) in December 1995; the Salt Lake City workshop on food-based approaches to preventing micronutrient malnutrition, organized by Cornell University and cosponsored by Food and Agriculture Organisation of the United Nations (FAO), UNICEF, and the Thrasher Foundation in November 1995; the Swedish Nutrition Foundation symposium on iron nutrition in health and disease in August 1995; the USAID/OMNI and Institute of Child Health workshop on iron interventions for child survival in May 1995; the WHO/UNICEF/United Nations University (UNU) consultation on indicators for assessing iron deficiency and strategies for its prevention in December 1993; and the United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition (ACC/SCN) workshop on controlling iron deficiency in June 1990.

ASSESSMENT AND ANALYSIS

IRON DEFICIENCY AND ANEMIA

Defining the Problem

Iron is essential in the production of hemoglobin, which functions in the delivery of oxygen from the lungs to body tissues, in electron transport in cells, and in the synthesis of iron enzymes that are required to use oxygen for the production of cellular energy (Bothwell et al. 1979; CEC 1993).

Iron balance is determined by the body's iron stores, iron absorption, and iron loss. At least two-thirds of body iron is functional iron, mostly hemoglobin within circulating red blood cells, with some as myoglobin in muscle cells and parts of iron-containing enzymes. Most of the remaining body iron is storage iron (existing as ferritin and hemosiderin) that serves as a deposit to be mobilized when needed. Adult men have about one-third of their total body iron as storage iron, whereas women have a much lower proportion (Yip et al. 1996a) because of menstrual blood loss in nonpregnant women and the requirements for fetal and maternal-tissue development of pregnant women. In most European countries, for example, at least 20–30% of women of reproductive age have no iron stores at all (CEC 1993). Young children also have low iron stores because of the use for iron for growth and expansion of blood volume (Dallman et al. 1980).

There are three main stages in the reduction of body iron.
1. **Iron depletion** is a decrease of iron stores, measured by a reduction in serum ferritin concentration. Although there is no evidence of any functional consequences of being iron deplete, it does represent a borderline state of iron nutrition in that any further reduction in body iron is associated with a decrease in the level of functional compounds such as hemoglobin.
2. **Iron-deficient erythropoiesis** develops only in the second stage when storage iron is depleted and iron absorption is insufficient to counteract the amount lost from the body through the feces, desquamated mucosal and skin cells, and menstrual blood loss among women. At this time, hemoglobin synthesis starts to become impaired and hemoglobin concentrations fall.
3. **Iron-deficiency anemia** is the most severe degree of iron deficiency and ensues if the hemoglobin concentration falls below a statistically defined threshold lying at two standard deviations below the median of a healthy population of the same age, sex, and stage of pregnancy (WHO/UNICEF/UNU 1996). By this stage, the restriction in hemoglobin production is severe enough to lead to the distortion of red cells, with microcytosis and hypochromia.

In this paper, the main outcome of concern[2] is iron-deficiency anemia because of the strong evidence relating it to various functional consequences (FAO/WHO 1988; Sloan et al. 1992) and its high prevalence in the developing-country populations that are the main focus of this review. It

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[2] Iron overload is another state of iron nutriture and is defined as an excess of body iron that, under certain conditions, may have harmful effects (BNF 1995). The practical significance of iron overload for iron-deficiency control programs is discussed in the Annex II.

is also the most common measure of iron status for which some data are available. Iron deficiency without anemia (that is, stage two) has also been related to certain deficits in physiologic function and is, therefore, clearly relevant too. The depletion of iron stores (stage one), as indicated by a low serum ferritin, however, is not in itself related to functional impairment (Bothwell et al. 1979; Dallman 1986; FAO/WHO 1988).

Iron-deficiency anemia represents one extreme state of the iron-deficiency spectrum. For every case of iron-deficiency anemia found in a population, there are thought to be at least two cases of iron deficiency (Yip 1994; WHO/UNICEF/UNU 1996).

Assessing Iron Status

This section contains only a brief description of the types of methods and approaches for population-based assessment, monitoring, and surveillance that are feasible in resource-poor situations in developing countries, where the problem of iron deficiency is invariably most pronounced. In such settings, the most common method for assessing iron status is through the measurement of hemoglobin (Hb) or hematocrit (Hct) levels as a measure of anemia. Moreover, these are probably the only feasible methods in most resource-poor settings.

Although anemia is not a specific indication of iron deficiency, given that other causes are possible (although usually less common), a population with a high prevalence of anemia is likely to have a high prevalence of iron deficiency (Yip et al. 1996b). The usual way to find out whether anemia is a result of iron deficiency is to monitor hemoglobin or hematocrit response to oral iron supplementation (Hallberg et al. 1993). A hemoglobin increase of 1 g/dL after 1–2 months supplementation is diagnostic of iron deficiency (WHO 1968).

Another concern is the fact that iron-deficiency anemia, representing as it does the extreme of the iron-deficiency problem, may not be a good predictor of iron deficiency where the latter is of low prevalence (Yip et al. 1996b), although such a situation is quite rare in most developing countries.

Hemoglobin distributions vary with age, sex, and different stages of pregnancy, and with altitude and smoking (CDC 1989) and possibly is genetically determined (Perry et al. 1992). Critical levels of hemoglobin and hematocrit with regard to age, sex, and physiologic status are provided in Table 1.

Through comparison of the hemoglobin distributions of subpopulation groups, it is possible both to circumvent problems of measuring only the anemia extreme of the iron-deficiency problem and, to some extent, to investigate etiology. If low intake of dietary iron or low iron bioavailability, or both, is a main cause, women and young children will be disproportionately affected compared to men (Yip et al. 1996b). If, on the other hand, anemia is largely due to malaria, hookworm, or infection, the hemoglobin distribution of both men and women will be skewed to the left.

The measurement of iron intake through dietary assessment is only useful as a complement to, not a substitute for, the direct measurement of hemoglobin concentrations, because iron intake and iron nutritional status are usually poorly correlated when bioavailability and host factors are not

Table 1. Hemoglobin and hematocrit levels below which anemia is judged to be present.

Group/age/physiologic status	Critical level	
	Hemoglobin (g/dL)	Hematocrit (%)
Children		
6 months to 5 years	11.0	33.0
5–11 years	11.5	34.0
12–13 years	12.0	36.0
Men	13.0	39.0
Women		
Nonpregnant	12.0	36.0
Pregnant	11.0	33.0
Severe anemia	7.0	–
Very severe (life threatening)	4.0	–

Source: WHO/UNICEF/UNU (1996), adapted from WHO (1968).

accounted for. Dietary assessment may, however, be useful for infants who consume few other foods in a predominantly milk-based diet.

The determination of hemoglobin concentrations can be done in the field by using a HemoCue (Van Schenck et al. 1986) based on the laboratory-based cyanmethemoglobin method of assessment. The HemoCue is a battery-operated photometer with disposable cuvettes that is portable, durable, reliable, accurate, and simple to use, without need for laboratory support. It costs about US$500 with each cuvette costing US$0.90. However, the recurrent expense of replacing the nonreusable cuvettes may be prohibitive for routine community-based assessment in many countries. Reusable cuvettes have been considered but are problematic because residual water may possibly dilute the blood and because of concern over safety with respect to AIDS (acquired immune deficiency syndrome). The need for a simple test remains: one that can be carried out by community-based workers for population-based assessment and monitoring of iron status.

The hematocrit or packed cell volume (PCV) method is also simple, although more variable than hemoglobin assessment, and can be done using a hand-cranked microcentrifuge. Although it can be used where the HemoCue method is not feasible, there is little advantage in carrying out both hemoglobin and hematocrit assessments at any one time.

Serum ferritin is the most specific biochemical test indicator of total body iron stores and is a useful indicator of iron status where prevalence of iron-deficiency anemia is low. However, serum apoferritin is an acute-phase reactant protein that is elevated in response to infection — thus constraining interpretation in environments where the incidence of infection is high (WHO/UNICEF/UNU 1996). Moreover, there is no current simple method for field-based testing.

There is an entire battery of biochemical tests that can be conducted for individual assessment in research or laboratory settings: most of them are neither feasible nor necessary in field conditions

in developing countries. Other recent papers — and notably the forthcoming WHO/UNICEF/ UNU (1996) report of an expert consultation — give full descriptions of these tests and their relative utility in different situations.

PREVALENCE

When attempting to assess the magnitude of the problem, globally, regionally, or nationally, the first problem encountered is the general paucity of data on anemia. The prevalence data by country that do exist, moreover, are often confined to pregnant women, who are likely to be the group most at risk: but not the only one. Inevitably, the design of any relevant action will be constrained by a lack of understanding of how many people are affected, who they are, and to some extent why they are anemic.

Over 2 billion people worldwide are iron deficient, as mentioned earlier, with a total prevalence estimated at about 40% of the world's population (WHO 1991). Prevalences among various subgroups are estimated (in descending order) at: 51% for pregnant women, 48% for infants and 1- to 2-year-old children, 35% for nonpregnant women, and 25% for preschool children. These are global mean estimates — prevalences in all these subgroups tend to be up to three to four times higher in developing than developed countries.

Recent regional data from WHO (1996), derived from a total of 32 existing national-level surveys available globally, show the following ranked prevalences of anemia (hemoglobin <11 g/dL) for pregnant women: South-East Asia (79%), Eastern Mediterranean (61%), Africa (44%), Western Pacific (39%), Americas (29%), and Europe (20%). In Central Asia, very high prevalences among women (about 80%) and children (about 60%) have recently been reported in demographic and health surveys in Kazakhstan and Uzbekistan. Nearly half of the global total number of anemic women live in the Indian subcontinent (WHO 1991) and, in India alone, prevalence of anemia among pregnant women may be as high as 88% (ICMR 1989). Among adult women, the trend in anemia in the last two decades or so is one of deterioration in all regions except South America, the Near East, and North Africa (ACC/SCN 1992). Again, however, data are scarce.

Prevalence data from other age groups are often not available. Figures for infants and very young children are usually similar to those among pregnant women, whereas prevalences among school-aged children in developing countries have been estimated at about 40% (WHO/UNICEF/UNU 1996).

In a multicountry study on nutritional status of adolescents carried out by the International Center for Research on Women, anemia was found to be the most widespread nutritional problem and highly prevalent in four of the six studies in which it was assessed: prevalences ranging from 32–55% (Kurz and Johnson-Welch 1994). There was no gender difference in three of four studies in which it could be assessed, whereas in the fourth more boys than girls were anemic. Based on the few data available at that time on anemia during adolescence, DeMaeyer and Adiels-Tegman (1985) had earlier estimated the mean prevalence in developing countries at 27% with no gender difference.

A classification of countries with respect to the degree of public-health significance of anemia has been proposed (WHO/UNICEF/UNU 1996), in which countries or population groups with anemia prevalence of at least 40% are categorized as "high," 15–40% as "medium," and under 15% as "low." These rates apply to all age and physiological groups. This classification has, however, been opposed by some on the grounds that it implies that nearly 100% of the population need to be iron deficient before the problem is considered highly significant.

REQUIREMENTS

Iron requirements differ with age, gender, and physiologic state (Table 2). To move from these values for median requirements for absorbed iron to recommendations for dietary intakes, it is customary to account for two important facts.

First, requirements differ between seemingly similar individuals. Thus, for example, although the median menstrual loss of iron in women is shown as 0.48 mg/day, 5% of women lose more than 1.6 mg/day and their needs for absorbed iron are correspondingly increased. For the males and nonmenstruating females of all ages, it was estimated that only about 2.5% have needs above the median plus 30%. An allowance for this individual variability is then included in the commonly reported recommended dietary allowances (RDA).

Second, and perhaps more importantly, to move from needs for absorbed iron to needs for dietary iron, the proportion of dietary iron that can be expected to be absorbed must be considered. This is a function of both the nature of the diet and the levels of iron in the body. Thus, for example, the 1988 FAO/WHO committee defined two states of iron nutriture that could be seen as practical goals in developing countries and three classes of diet. For diets based largely on cereals, roots, and tubers with negligible quantities of meat, fish, or foods rich in ascorbic acid, as might characterize the situation of many developing countries, it was estimated that only about 5% of the dietary iron would be absorbed when iron status was adequate to maintain normal iron transfer to tissues and prevent all clinically detectable functions but not maintain any iron stores. At a state of iron nutriture adequate to prevent anemia but not necessarily maintain normal red cell formation rates, utilization was estimated to increase to 7.5%. In these two situations, the need for absorbed iron would be multiplied by 20 and 13, respectively. If one wished to maintain normative levels of iron storage, in addition to supporting all recognized functions of iron, the use of dietary iron was expected to fall to only about 2.5% and the adjustment factor would increase to about 40.

The last column in Table 2 shows a calculation of the ratio of median iron need to median energy need. It illustrates (FAO/WHO 1970) that if all members of a household ate the same mix of foods in quantities that satisfied their energy needs, the subjects most likely to be affected by inadequacy of the concentration of iron in that diet would be pregnant women, nonlactating menstruating women, and infants in the second half of their 1st year of life. The physiological factors creating this situation are the effect of rapid "growth rates" in infants and the equivalent in pregnant women, and the high blood losses of menstruating women (FAO/WHO 1970; Beaton 1974; Bothwell and Charlton 1981; Viteri 1996c). Although not illustrated in this table, major infection of hookworm can result in blood losses equivalent to those seen in menstruating women

Table 2. Median requirements for absorbed iron (mg/day) at different stages of the life cycle.

Group	Age (years)	For growth[a]	Basal losses[b]	Menstrual loss	Total (mg/day)	Ratio (mg/1,000 kcal)[c]
			To replace —		Total median iron need	
Infants	0.25–1	0.56	0.21	–	0.77	0.98
Children						
Preschool	1–2	0.24	0.25	–	0.49	0.42
Preschool	2–3	0.22	0.34	–	0.56	0.36
School-aged	6–12	0.38	0.56	–	0.94	0.40
Adolescents						
Girls	12–16	0.36	0.79	0.47	1.62	0.76
Boys	12–16	0.66	0.80	–	1.46	0.58
Adult men	17–45	–	0.91	–	0.91	0.31
Adult women						
Nonpregnant	17–45	–	0.77	0.48[d]	1.25	0.59
Pregnant[e]						
First trimester	–	0	0.77	0[f]	0.77	0.33
Second trimester	–	0.83[g]	0.77	2.75	4.35	1.89
Third trimester	–	2.75[g]	0.77	2.75	6.25	2.72
Lactating	–	–	1.05[h]	–	1.05	0.40
Postmenopausal	45 +	–	0.77	–	0.77	0.41

Source: Modeled after FAO/WHO (1970) and updated to iron requirements from FAO/WHO (1988) and energy requirements from FAO/WHO/UNU (1985). See FAO/WHO (1970) for discussion of implications.

a No provision is made for development of iron stores; no storage expected in adults.
b Basal losses in urine, skin, and feces.
c Based on estimated energy intake for intermediate activity, for different age–sex categories, as calculated in FAO/WHO/UNU (1985).
d 25% women lose >0.8 mg iron per day, 10% >1.3 mg, and 5% >1.6 mg.
e For a 55-kg woman.
f Blood volume.
g Fetus and placenta.
h Comprises basal losses of 0.77 mg/day plus losses in breastmilk.

and can easily make adult men and children as sensitive to dietary iron supply as the foregoing groups (Beaton 1974). Current estimates of iron requirements of pregnant women are so high that the 1988 committee felt they could not, under any expected circumstances, be met by usual diets, even in industrialized countries. The committee did not offer dietary recommendations for pregnancy (FAO/WHO 1988).

Pregnancy

The pregnant woman is particularly at risk of becoming anemic, having high iron needs because of increased blood volume and the growth of the fetus, placenta, and other maternal tissues. In late

pregnancy, her iron needs will rise to up to five times her prepregnancy requirement — an amount in excess of what could be provided by food, even if fortified, and only partially compensated for by increased iron absorption because of low body stores (Yip et al. 1996a).

As may be calculated from Table 2, the total iron cost of pregnancy for a 55-kg woman, assuming 93 days per trimester, is 845 mg, which is entirely concentrated in the second (333 mg) and third (512 mg) trimesters. The net additional iron required for pregnancy, that is, subtracting the iron requirement of a nonpregnant, menstruating woman, is 711 mg or 2.5 mg/day throughout the whole pregnancy. Women without iron stores, or with minimal stores, going into pregnancy will require supplements to avoid the impairment in synthesis of the amounts of hemoglobin required (FAO/WHO 1988).

However, if, for example, a mobilizable store of 250 mg iron could be established in nonpregnant women — that is, the estimated mean storage iron among North American women (FAO/WHO 1970) — then the additional iron from exogenous sources during pregnancy would fall to about 711 - 250 = 461 mg or 1.7 mg/day. This is about the same as the daily requirement of a menstruating woman in the 95th percentile, and suggests that if such a store could be established before pregnancy, then dietary approaches including fortification, if successful, might suffice to meet the iron needs of a pregnant woman (Beaton, personal communication[3]) This was recognized in the FAO/WHO committee report (FAO/WHO 1970), which stated:

> The Group was of the opinion, therefore, that for women whose iron intake throughout life has been at the level recommended in this report, the daily intake of iron during pregnancy and lactation should be the same as that recommended for non-pregnant and non-lactating women of childbearing age.

Infancy

The full-term newborn baby has iron stores at birth that are usually sufficient, along with the highly bioavailable iron from breast milk, for the first 4–6 months if the mother was healthy. Mild maternal iron deficiency and anemia have few significant repercussions on the iron status of the newborn, but severe anemia does (NAS 1991).

The risk of an infant developing iron deficiency is heightened by the practice of premature clamping of the umbilical cord because this deprives the infant of an additional one-third of his/her total blood volume. Delaying ligation of the umbilical cord until 1 minute after it has stopped pulsating, can significantly increase blood volume and iron reserves of the newborn (Grajeda et al. 1997). The cord should not be milked and the newborn should be held below or at the level of the placenta to prevent the risk of polycythemia (a result of too many blood cells).

In the first 2 months of life, there is minimal dietary iron absorption and stores are mobilized to meet the iron requirement (FAO/WHO 1988). Thereafter, dietary iron absorption becomes increasingly significant and, by about 4–6 months of age, iron stores have been significantly

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[3] Beaton, G.H., 12 July 1997; GHB Consulting, 9 Silverview Drive, Willowdale, ON, Canada M2M 2B2.

depleted and the diet now becomes critically important (see *To What Extent Can the Diet Support Adequate Iron Nutriture?* page 37).

A low birth-weight baby will have low iron reserves and require extra iron from 3 months of age, implying the need for supplemental iron drops, which are in addition to and fully compatible with exclusive breastfeeding for the first 6 months (WHO/UNICEF/UNU 1996).

Although iron is not highly concentrated in breast milk, it is highly absorbed. Iron bioavailability from breast milk has been reported as being about 50% compared to 10% from cow's milk and infant formulas (Lonnerdal 1984). During exclusive breastfeeding, any residual postpregnancy maternal iron deficiency can be alleviated to some extent by lactational amenorrhea as the amount of iron secreted in breast milk is less than that which would be lost if menstruation had resumed (FAO/WHO 1970; CEC 1993).

Iron deficiency among infants is most prevalent among 6- to 12-month olds or 1- to 2-year olds when 70% and 50% of the respective requirements arise from the rapid rate of tissue growth (FAO/WHO 1988). In the 1st year of life, an infant's requirement for absorbed iron is comparable to that of an adult man, which is very difficult to fulfil, given that iron intake tends to be proportional to energy intake, which in turn is proportional to body size. On a per-kilogram body-weight basis, infants will require three times as much absorbed iron as adult men (FAO/WHO 1988; last column of Table 2), which points to the need for the iron concentration in the infant diet to be similarly elevated. In practice, however, the first foods that infants consume tend not to be favourable for iron absorption (see *To What Extent Can the Diet Support Adequate Iron Nutriture?* page 37).

Other Vulnerable Stages

The risk of iron deficiency is proportional to growth velocity and is thus much lower for children of 2 years or older. During the adolescent growth spurt, the risk reappears for both boys and girls (Dallman et al. 1980), after which it subsides for boys but remains for girls because of menstrual blood loss. In old age, another peak in risk may occur associated with underlying chronic disease (Joosten et al. 1992).

CAUSES

The main causes of iron-deficiency anemia are merely summarized here.[4] Greater detail on causality, to the extent that it determines the type of appropriate remedial action, is provided in *Strategies* (see pages 22–60). Iron-deficiency anemia is largely caused, at an immediate level, by the following factors:

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[4] The Micronutrient Initiative (MI) recently organized an Expert Consultation on the Determinants of Anemia in Ottawa, 16–17 September 1997, that aimed to fully investigate the etiology of anemia and the various interactions between contributory causes, at different stages of the life cycle, in different regions. A report will be available in 1998.

- Poor bioavailability of iron consumed: related to a low consumption of absorption-enhancers and a high consumption of absorption-inhibitors;
- Insufficient quantity of dietary iron intake in relation to need, to a lesser extent;
- Increased requirements at certain stages in the life cycle, notably during pregnancy and during rapid early childhood and adolescent growth; and
- Blood loss due to both menstruation and childbirth among women, amplified by repeated and closely spaced pregnancies; and parasites, most importantly hookworm but to a lesser extent *Schistosoma* in some regions, whipworm, and amoebiasis.

Although most anemias in most situations have an iron-deficiency component, other contributing factors (which may overlap significantly with iron deficiency, particularly with respect to severe anemia) include deficiencies of folate, vitamins A and B-12 (see *Other dietary constituents*, page 34), and genetically determined hemoglobinopathies such as thalassemia and sickle-cell disease.

In addition, infections, especially chronic and recurrent infections, can interfere with food intake and the utilization of iron. There is also a nonspecific effect of the infectious process on hematopoeisis that manifests itself in falling hemoglobin levels and possibly anemia. Such infections include chronic diarrheal disease, malaria, and, more recently, human immunodeficiency virus (HIV) (Hershko et al. 1988; Brabin 1992). Malaria in particular is a very widespread and highly significant contributing factor to severe anemia in sub-Saharan Africa (Fleming 1989a, 1991). In fact, anemia in Africa tends to have multiple and interacting etiologies including malaria; deficiencies of iron, folate, protein, and possibly other micronutrients such as vitamin A and riboflavin; and pyogenic infections, sickle-cell disease, and now AIDS (Fleming and Werblinska 1982; Fleming 1989b).

Beyond such immediate-level causes, as with any other nutritional problem in society, there are clearly important underlying causes. These include the ability of households to acquire sufficient food of acceptable quantity and quality for all household members throughout the year, the capacity and practice of adequate care for women and children, and the access of households to good quality health services and a healthy environment. Underpinning such factors, at an even more basic level, poverty, the low status of women, illiteracy, and environmental degradation are critically important.

CONSEQUENCES

The main consequences of iron-deficiency anemia are described in this section, including those relating to maternal mortality risk, fetal growth retardation, prenatal and perinatal mortality, compromised mental development, growth failure and poor physical development of young children, lowered physical activity and labour productivity, and increased morbidity.

Maternal Mortality Risk

Anemia is a major contributory cause of postpartum maternal mortality, and may "shift a pregnant woman's balance towards death" during delivery (Koblinsky 1995). A recent review of 21 studies in Africa and Asia (Ross and Thomas 1996) concluded that a reasonable estimate of the risk of

maternal mortality attributable to anemia is 20.0% in Africa and 22.6% in Asia. These are deaths that would have been avoided if the mother were not anemic. The values are composites of direct anemia-related mortality (7.6% and 10.8% in Africa and Asia, respectively) plus indirect anemia-related mortality (that is, 25% of all hemorrhagic deaths plus 10% other maternal deaths[5]). Direct anemia-related mortality is due to heart failure, shock, or infection that has taken advantage of the woman's impaired resistance to disease (Royston and Armstrong 1989).

The figure of 20% plus is seen as a conservative estimate because these were deaths occurring only in hospitals where
- Attempts were made to prevent death and
- Anemia-related emergencies would be under-represented to the extent that fatigue and lethargy prevented at-risk women reaching the hospital.

Other factors preventing women reaching the hospital in time include traditions of home birthing, lack of funds for maternity fees, nonavailability of transport, and lack of information on where to go. Anemia-related lethargy is also associated with prolonged labour and related sepsis postpartum (Kusin, personal communication[6]).

It is not only severely anemic women who are at risk of dying during childbirth. Maternal mortality risk has been seen to decrease as hemoglobin levels increase (Harrison 1982) and this has recently been corroborated by evidence from Kenya and the USA. In the Kenyan study, decreasing mortality rates in hospital were strongly associated with increasing hemoglobin values, and the attributable mortality due to severe anemia was 31%, with severely anemic women having an 8.2 increased odds of mortality than nonanemic women (Zucker et al. 1994). In a study of the effect of anemia on surgical mortality in the USA, a similar relationship was found, and even mild anemia was associated with some increase in mortality risk (Carson et al. 1996).

Fetal Growth Retardation and Prenatal and Perinatal Mortality

Anemia is directly related to risk of preterm delivery, inadequate gestational weight gain, and increased perinatal mortality (MacGregor 1963; Garn et al. 1981; Murphy et al. 1986; Worth-ington-Roberts 1990; Scholl et al. 1992). The more severe the anemia, the greater is the risk that the mother will deliver a low birth-weight baby because of poor intrauterine growth. A US study found a progressive reduction of favourable pregnancy outcomes by 30% as hemoglobin at mid-term declined from 10.5 g/dL to 8.0 g/dL (Garn et al. 1981). Even mild anemia has been related to placental hypertrophy and raised risk of low birth weight (Hemminki and Rimpella 1991).

The association between anemia and both preterm delivery and intrauterine growth retardation is strongest in early pregnancy or at least before midterm, suggesting that prepregnancy improve-

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[5] These latter two percentages for deaths indirectly attributable to anemia are based on assumptions that the authors state are "somewhat arbitrary but can be defended as approximations when the prevalence of maternal anemia is high" (Ross and Thomas 1996).

[6] Kusin, J., 3 September 1996; Royal Tropical Institute, Mauritskade 63, 1092 AD Amsterdam, The Netherlands.

ments in iron status are warranted (Klebanoff et al. 1988, 1991; Mohammed and Hytten 1989; Scholl et al. 1992; Scholl and Hediger 1995).

It is well known that low birth-weight babies have a higher risk of dying in infancy and early childhood (Villar et al. 1990). There is also increasing evidence of a heightened risk of coronary heart disease in later life, as suggested by studies in the UK (Barker 1993) and, more recently, in South India (Stein et al. 1996). Severe maternal anemia has been associated with increased child, as well as maternal, mortality (Van den Broek et al. 1993).

Evidence of a positive effect of supervised iron supplementation to malnourished pregnant women on anemia prevalence and low birth-weight incidence comes from several Indian studies (Sood et al. 1975; Agarwal et al. 1991).

Compromised Development in Young Children

Iron is present in key enzymes in several neurotransmitter systems in the brain; for example, the dopamine and serotonin systems (CEC 1993). Damage to the fetal brain arising from maternal anemia takes place early in pregnancy (Agarwal and Agarwal 1991), and there is evidence from animal studies to suggest that anemia in pregnancy is more damaging than anemia during lactation (Felt and Lozoff 1996).

The peak prevalence of iron deficiency among young children coincides with the latter part of the spurt in brain growth (6–24 months) when motor and cognitive abilities take shape (Martorell 1997). Only 10% of the iron content of the brain is present at birth and 50% at age 10, but it continues to increase up to the age of 20–30 years (CEC 1993). Most studies show that children with iron-deficiency anemia perform less well on psychomotor tests than nonanemic counterparts (Pollitt and Metallinos-Katsaras 1990). The magnitude of deficit is as much as one standard deviation, which is greater than that associated with mild lead poisoning in childhood and similar to that caused by mild–moderate iodine deficiency (Yip 1996a).

An infant who becomes anemic through iron deficiency is at high risk of long-term, even permanent, impairment in mental and motor development (Lozoff 1990; Lozoff et al. 1991). For infants, there is only one reliable study that shows improvement in developmental test scores after iron administration — suggestive of a causal association (Idjradinata and Pollitt 1993).

Among the conclusions of an expert consultation on the role of iron status in the development of children, convened by USAID, OMNI, and the Partnership for Child Development (PCD) at Oxford in September 1996, were the following (Draper 1997):

- Iron deficiency without anemia has not been associated with any of the mental, motor, and social–emotional disturbances observed in infants with iron-deficiency anemia.
- Most studies of iron therapy in infants and young children (less than 2 years old) reported no improvement in either mental or motor development of anemic infants after either short- or long-term treatment.
- Preschool children (2–4 years old), however, displayed marked improvement after successful iron supplementation, consistently eliminating the learning problems associated with anemia.

There is some evidence that poorer performance of anemic infants later on in the preschool and school-age periods in these studies is more likely to be a result of poor socioeconomic status, and especially fewer years or lower grades in maternal education (Palti et al. 1983; Deinard et al. 1986). Moreover, there is no assurance that the poorer test scores of such young children are a reflection of this anemia in infancy, and it is possible that intervening and undocumented periods of anemia are responsible for the lower scores.

In sum, the evidence for a causal association between anemia in infancy and lower developmental scores is only suggestive. Only two preventive trials have been carried out to date. One failed to demonstrate that anemic infants given prophylactic iron supplementation after 6 months will show improved developmental scores over untreated controls (Lozoff et al. 1996) while the other, conducted among infants who were more socioeconomically disadvantaged, did demonstrate such benefits (Moffatt et al. 1994). An adverse effect of iron-deficiency anemia on mental development may only be manifested where infants are already at risk from other biological, environmental, or social factors and the benefits of prevention may be more likely to be seen in such children.

One study has shown that anemic infants on reaching school age, even if no longer anemic, average 8.8 points lower in IQ (intelligence quotient) than nonanemic controls (Palti et al. 1983). At age 10, a child who was anemic as an infant may have poorer reading and writing skills and lower performance both academically and physically (Walter and de Andraca 1996).

Mental development is hindered through several interacting routes, not just damage to the brain (Brown and Pollitt 1996). These include interactions between ill health, low activity because of lethargy (which minimizes exploration), and poor rates of growth and motor development (which result in lowered parental expectations of a child who still appears small). Lethargy and ill health in a child may, moreover, result in increased mother–child attachment and the elicitation of less stimulation from caregivers (Lozoff et al. 1986)

Finally, iron deficiency adversely affects the ability of school children and adolescents to learn too. The USAID/OMNI/PCD consultation concluded (Draper 1997) that "iron supplementation resulted in significant improvement in school measurements of verbal and other measurable skills among primary school children and adolescents." This has been further corroborated by a recent study of female adolescents in the USA where nonanemic, iron-deficient 13- to 18-year-old girls were found to have significantly better verbal learning and memory after 2 months of iron supplementation (Bruner et al. 1996). A study in Israel, among 16- to 17-year-old girls, had earlier found that iron supplementation for 2 months resulted in reduced lassitude and improved ability to concentrate (Ballin et al. 1992).

Child Growth Failure and Poor Physical Development

Severe maternal anemia, unlike mild, does lead to fetal iron deficiency and lower fetal iron reserves, a problem magnified by the likelihood of low birth weight (Nhonoli et al. 1975; Singla et al. 1978; Viteri 1994). Such infants require more iron than can be supplied by breast milk alone by age 2–3 months (Llewellyn-Jones 1965). Children born of iron-deficient, anemic mothers have been found to have a significantly higher risk of being iron deficient or anemic by their first birthday (Colomer et al. 1990).

The child has a particularly high risk of iron deficiency from 6–24 months of age when growth velocity is particularly high, the consequences of which could be impaired energy utilization and physical growth (Judisch et al. 1986). The high-risk period for developing iron deficiency (that is, when incidence is high) is actually the 6- to 12-month age group. Iron deficiency may then persist through the 2nd and later years as a high prevalence. Children 6–8 years of age with low iron stores have been found to be significantly more stunted than their more iron-replete counterparts in a study in South Africa (Kruger et al. 1996). Also, the fact that growth of iron-deficient preschool and school-age children has been found to improve after iron supplementation (Aukett et al. 1986; Chwang et al. 1988; Briend et al. 1990; Latham et al. 1990; Angeles et al. 1993; Lawless et al. 1994) is further indirect evidence of the growth-inhibiting effect of iron deficiency (Bhatia and Seshadri 1993; Allen 1994). It is not clear whether this is an independent effect of iron because appetite, and possibly food intake, also increase as iron deficiency is corrected (Lawless et al. 1994).

One study has suggested that the rate of weight gain of 12- to 18-month-old, iron-sufficient Indonesian children may be reduced with long-term daily iron supplementation (Idjradinata et al. 1994), although no reduction in linear growth occurred — suggesting that any such negative effect was not significant.

Lowered Physical Activity, Mental Concentration, and Productivity

Energy metabolism, particularly in muscle cells, is impaired by iron-deficiency anemia as is the ability of blood to transport oxygen around the body, particularly in intense activity (Davis et al. 1984). Work capacity, and hence in many cases earning capacity, of adults is considerably reduced by anemia (Viteri and Torun 1974; Basta et al. 1979; Bothwell and Charlton 1981), and this appears to be a linear relationship (Viteri and Torun 1974).

As well as anemia, effects have been seen in nonanemic women with iron depletion. In a US study, iron-depleted nonanemic women were found to have significantly reduced levels of maximal oxygen consumption (an indicator of aerobic capacity) when compared to a matched iron-sufficient group. The reduction associated with iron depletion was thought to be related to reduced body storage and was not related to decreased oxygen transport capacity of the blood (Zhu and Haas 1997).

Lowered attention span (see *Compromised Development in Young Children*, page 16) will adversely affect mental concentration, which can further reduce productivity. If such a loss in productivity is combined with the high existing prevalences of anemia, the potential effect of anemia on the national economic output can be seen to be substantial.

In addition to losses in waged work, a recent study among female loom workers in Indonesia has shown that anemic women spend 1 hour per day less in domestic work than nonanemic coworkers (Scholz et al. 1997). It is also likely that anemic caregivers are less able to provide their children with appropriate levels of stimulation to fulfil their physical and cognitive potential.

The effects are reversible and iron supplementation has been shown in many studies to lead to increases in work output and gains of 10–30% in productivity and take-home pay (for example, Basta et al. 1979; Edgerton 1981; Hussaini et al. 1981; Vijayalakshmi et al. 1987).

Increased Morbidity

Iron deficiency may adversely affect specific cell-mediated immunity, even before frank anemia (Bhaskaram and Reddy 1975; Srikantia et al. 1976; Stinnert 1983) as well as nonspecific immunity related to oxygen-dependent defense mechanisms. Lowered resistance manifests itself in increased morbidity (both incidence and severity) from diarrheal, respiratory, and other infections (Andelman and Sered 1966; Basta et al. 1979; Hussein et al. 1988). Subsequent raising of iron status of iron-deficient children through supplementation or fortification can reduce morbidity (Enwonwu 1990)

Other Consequences

When exposed to cold, those suffering from iron-deficiency anemia may be at higher risk of hypothermia because of reduced thyroid function and altered epinephrine and prostaglandin production and metabolism (Dillman et al. 1982; Beard and Borel 1988; Martinez-Torres et al. 1984). Altered thyroid function may also affect conversion of provitamin A to vitamin A in the intestine.

Iron deficiency is also associated not only with increased absorption of iron (Watson et al. 1980; Andelman and Sered 1982; Yip 1990), but also of other toxic heavy metals including lead and cadmium. Children living in polluted urban environments will be particularly at risk. The microcytic anemia thought in the past to be due to lead poisoning is, in fact, iron-deficiency anemia, which is particularly common among lead-poisoned children (Clark et al. 1988). Iron treatment may also reduce lead poisoning (Ruff et al. 1993).

Finally, iron deficiency has also been associated with altered gastrointestinal function relating to malabsorption of vitamin D (Heldenberg et al. 1992) and fat (Naiman et al. 1964).

STRATEGIES

INTRODUCTION

Iron status may be improved through food-based strategies (primarily fortification and dietary modification) and nonfood-based strategies (primarily supplementation and parasitic disease control). The role and potential of these four main approaches, experiences with their implementation along with the important major remaining issues in ensuring their effectiveness are described in this section.

Iron supplementation is covered first as it is particularly important in preventing and correcting anemia among those population subgroups at highest risk, such as pregnant women. **Dietary modification** is then discussed to clearly describe the potential of the diet for fulfilling iron needs at various stages of the life cycle. Third, **fortification** considers the potential over time of approaches for adding iron to the diet, the current status of program development, and remaining challenges. Fourth, the contribution of **parasitic diseases**, including hookworm and malaria, to the anemia problem and appropriate approaches for their prevention and control are described. Finally, the relative **costs and benefits** of different approaches are briefly described although recognizing that costs are situation-specific and the full range of benefits are hard to capture.

SUPPLEMENTATION

Pharmaceutical iron supplementation, which involves the provision of iron (usually as ferrous sulphate) in capsule, tablet, or elixir form is the most common strategy for the control of iron-deficiency anemia. It may, moreover, be the only feasible option when the iron requirement is high over a relatively short time, for example, during pregnancy. Iron supplementation generally has three main objectives that largely correspond with the three stages of progressive iron deficiency (see *Defining the Problem*, page 6), although these objectives are often not made explicit:
* To correct preexisting iron-deficiency anemia;
* To prevent iron deficiency leading to anemia; and
* To prevent the development of iron deficiency.

The great majority of iron supplementation programs worldwide are focused on achieving the first objective, primarily among pregnant women. The prevailing philosophy remains one of therapy or correction ("cure"), rather than prevention. In this section, the role of supplementation at different stages of the life cycle, and what is known of its efficacy in small-scale trials and effectiveness in large-scale environments, is described before moving on to consider options for improving effectiveness.

Pregnant Women
The elevated iron requirement of pregnant women (see *Pregnancy*, page 11) indicates the need for increasing prepregnancy reserves (that is, during adolescence and between births) and providing iron supplements during pregnancy (Table 3). Although food-based strategies are important for raising the iron status of populations, they will not be enough for many iron-

Table 3. Recommended iron supplementation doses and schedules.[a]

Vulnerable group	Recommended iron dose and schedule
Infants and young children	2 mg/kg body weight daily from 6 to 24 months. If low birth weight, start at 3 months of age
Preschool children (2–5 years) with IDA[b]	2 mg/kg body weight, daily (up to 30 mg)
School children and adolescent girls with IDA	60 mg/week with 0.35 mg folic acid, or 30 mg/day with 0.35 mg folic acid
Women of childbearing age with IDA evidence	60 mg/day with 0.35 mg folic acid
All pregnant women	60 mg/day with 0.40 mg folic acid starting as soon as possible after 3rd month of gestation
Lactating women	Continue with weekly 60 mg doses plus 0.40 mg folic acid between pregnancies

Source: WHO/UNICEF/UNU (1996).

a Detailed protocols for the use of iron supplements to prevent or correct anemia, for different age–sex and physiologic groups, are available in recent publications (Stoltzfus and Dreyfuss 1997; WHO/UNICEF/UNU 1996).

b IDA = iron-deficiency anemia.

deficient women who become pregnant (Bothwell and Charlton 1981; FAO/WHO 1988). The minority of women in developing countries who have stores of at least 250 mg of iron on becoming pregnant may meet their iron requirements without resort to supplements if they consume a dietary mix that provides the equivalent of about 1.7 mg absorbed iron per day (see *Pregnancy*, page 11). This, for example, equates with about 34 mg iron per day from a cereal-based diet with low iron bioavailability: in India, where such a diet is the norm, adult women tend to consume 23–30 mg per day (FAO/WHO 1988). The majority of women in developing countries do not have such iron store levels (for example, Franzetti et al. 1984). Routine iron supplementation during pregnancy will, thus, remain essential until dietary modification and fortification approaches have succeeded in raising the prepregnancy level of iron stores.

In a meta-analysis of clinical studies between 1966 and 1983, iron supplementation (starting at least before week 30 of pregnancy) was found to be highly efficacious in reducing the prevalence of anemia at term (Mohammed and Hytten 1989). In another meta-analysis of 24 randomized controlled trials, efficacy was also clearly demonstrated in correcting maternal anemia (Sloan et al. 1992). Other important findings derived from these two meta-analyses included:

- The first two trimesters are particularly important with respect to several outcome parameters.
- There was a dose–response and a duration–response relationship up to thresholds of about 60 mg iron daily dose and 20 weeks duration, respectively.
- Short-term, large-dose supplementation is relatively inefficient and ineffective and cannot substitute for longer-term, smaller-dose supplementation.

- Folate administration alone is associated with some reduction in anemia, but this is not significant.
- Among poorly nourished women, folate supplementation has been found to be associated with a reduction in prevalence of low birth weight.

Where the prevalence in pregnant women is at least 30%, which includes most developing country situations, the Joint UNICEF/WHO Committee on Health Policy (JCHP 1996) has recommended supplementing all pregnant women and children of 6 months to 5 year of age.

Nonpregnant Women and Adolescent Girls

Although most effort in the past has focused on controlling the anemia of pregnant women who can be reached through the health system, a more preventive approach is also needed to raise iron stores of women before they become pregnant or between pregnancies. Borderline iron stores before conception are the main cause of iron-deficiency anemia during pregnancy (Brabin and Brabin 1992). Many studies have shown a highly positive, significant correlation between hemoglobin concentrations at early or midpregnancy and those at term — with or without the presence of iron supplementation (for example, Sood et al. 1975; Charoenlarp et al. 1988; Ekstrom et al. 1996).

It is clearly not very efficient to deal with the problem of anemia among women by relying solely on trying to correct it during the short period of pregnancy when demand for iron is maximal. Such a strategy is undertaken to some extent because it has always been done this way and rarely evaluated, because anemia is widely perceived solely as a public-health or medical problem to be dealt with only by health services, and because pregnant women are deemed to be "reachable" through antenatal services, whether those services are actually accessible to women and used by them, or not. The statistics in *Prevalence* (page 9) demonstrate the ineffectiveness of a sole reliance on such an approach.

In addition to immediate benefits (see *Consequences*, page 14), raising iron status of adolescent girls will improve future iron status during the first pregnancy. Iron and folic acid supplementation is one of the most important direct interventions in nutrition for adolescent girls, given the lack of proven efficacy of food supplementation interventions for improving adolescent nutritional status (Gillespie 1997a). Folic acid is included within the supplement to prevent folate deficiency, which is implicated in the etiology of anemia and associated with neural tube defects in the newborn. Moreover, it might be too late to prevent neural tube defects by delaying folic acid supplementation until pregnancy — given the difficulty of early identification of pregnancy.

As well as improving adolescent iron status, supplementation may lead to improved growth. Iron and folic acid supplementation and antimalarial prophylaxis of pregnant Nigerian adolescents in the second half of pregnancy was found to increase their height and reduce the incidence of cephalopelvic disproportion (Harrison et al. 1985). Growth of prepubertal Kenyan schoolchildren was also found to be increased with iron supplementation (Latham et al. 1990) (see *Child Growth Failure and Poor Physical Development*, page 17).

Infants and Young Children

In most developing countries, 50% children are anemic by their first birthday (WHO 1991). Although breastfeeding should be sustained, breast milk will not suffice to fulfil an infant's iron needs after 6 months of age. Complementary foods, even if introduced on time, are likely to be low in iron content or bioavailability, or both (see *To What Extent Can the Diet Support Adequate Iron Nutriture?* page 37). Unless iron-fortified cereal is available and consumed, the main alternative in most parts of the world is to provide iron supplements for infants from 6 to 24 months of age (Yip 1994) where the prevalence of anemia is at least 20% (WHO/UNICEF/UNU 1996).

There is very little evidence to date of large-scale effectiveness of iron supplementation to young children. A trial in Romania demonstrated only a limited reduction in anemia prevalence of 6- to 9-month olds, with poor compliance being implicated (Ciomartan et al. 1995).

As the greatest risk lies in the 6- to 12-month age group, before the diversity of a child's diet (and hence iron intake and bioavailability) tends to increase, supplementation needs to be prioritized for this age group. Supplementing beyond this age, up to 15 months, may be sufficient to protect the child for the first 2 years, given the build-up of iron stores (Nestel and Alnwick 1997). Moreover, benefits may be long lasting — in a study of a group of iron-deficient under-5-year-old children in Indonesia, the majority had an adequate iron status 2 years after supplementation ceased (Angeles et al. 1995).

Liquid preparations are essential for children who cannot swallow tablets, but the tablets may be prone to deterioration in storage if vitamins are added, and precautions are needed against overdosing. A typical dropper bottle containing 30 mL of a concentrated aqueous solution of a soluble ferrous salt could safely provide sufficient iron for 2 months, thus necessitating just three trips to the health centre for a mother during the second 6 months of her child's life (Nestel and Alnwick 1997).

A joint USAID, OMNI, and UNICEF consultative meeting held in Copenhagen in 1996 discussed the issue of appropriate supplements for young children and options for multimicronutrient combinations. A list of available iron-based liquid formulations and their stability, dispensing instructions, and cost is being prepared by OMNI. In addition, this meeting recommended a thorough review of the history of the use of injectable iron for infants and its future potential when administered at lower doses, later in a child's life, using newer, safer compounds (Nestel and Alnwick 1997).

Even though preventive and therapeutic supplementation programs for infants have been recommended (INACG 1977; AAP 1992), no country has adopted these as national policy. Only India and some Caribbean countries have adopted a policy of preventive supplementation of vulnerable groups other than pregnant women, in this case preschool children (ICMR 1989; Gillespie et al. 1991).

If and when such a program is initiated on a large scale for 6- to 12-month-old children, there are likely to be considerable constraints to surmount including poor compliance, the relatively high cost of transporting the glass dropper bottles, problems with storage, and the difficulty of adding other micronutrients to an iron supplement (Nestel and Alnwick 1997).

Complementary Micronutrient Supplementation

Vitamin A supplementation at appropriate levels has been found in pregnant women and preschool and school-age children to improve iron metabolism as well as improving vitamin A status (Mejia and Chew 1988; Bloem et al. 1990; Suharno et al. 1993; Suharno and Muhilal 1996) and should be considered where iron deficiency is common. The anemia-reducing effect with a combined iron and vitamin A supplement has been found to be over 40% greater than that with an iron supplement alone (Suharno et al. 1993; Suharno and Muhilal 1996). A vitamin A sugar-fortification program in Guatemala resulted in improved iron status of the population (Mejia and Arroyave 1982), and a trial with vitamin A-fortified monosodium glutamate (MSG) in Indonesia increased hemoglobin levels among children (Muhilal et al. 1988). A similar effect has been seen in pregnant women at 26–28 weeks gestation (Panth et al. 1990). In a recent study in Indonesia, a supplement combination of iron, vitamin A, vitamin C, and folic acid provided weekly resulted in maximal increases of hemoglobin, retinol, and serum ferritin levels among adolescent girls (Schultink and Gross 1996). Formulations for young children should also account for vitamin A and other micronutrients in which the child may be deficient, such as zinc — although to date a suitable combined iron–zinc supplement has not been found in which the inhibitory effect of zinc on iron absorption on an empty stomach can be avoided (Schultink and Gross 1996). There is, however, evidence that taking combined iron–zinc supplements with meals will result in the inhibitory effect being avoided (Sandstrom et al. 1985; Rossander-Hulten et al. 1991) while no effect of iron administration was found on serum zinc or copper levels among healthy 1-year-old children (Yip et al. 1985). There remains, however, a need for a proper evaluation of indications of routine zinc supplementation before such a combined supplement program is initiated (Nestel and Alnwick 1997).

How Effective are Large-Scale Supplementation Programs?

Despite proven biological effectiveness or efficacy in small-scale trials, few large-scale supplementation programs have been found to be operationally effective to date. Operational effectiveness basically comprises coverage multiplied by compliance and is a measure of whether people in the real world beyond trials actually ingest supplements on a sufficiently regular basis. Most large-scale programs have not been evaluated with respect to impact. The main operational constraints identified in a review of six large-scale programs aimed at pregnant women (Gillespie et al. 1991) were:

* Inefficient and irregular supply, procurement, and distribution of supplements;
* Low accessibility and utilization of antenatal care by pregnant women;
* Inadequate training and motivation of front-line health workers;
* Inadequate counselling of mothers; and
* Low compliance by the intended beneficiaries with the supplementation regimen.

Supplementation programs thus share many of the problems that hinder primary health-care and essential-drugs programs in developing countries. Unlike the real world, many of these deficiencies can be avoided or rectified in supervised clinical trials. Efficacy in small-scale trials does not readily translate into effectiveness in large-scale programs. Iron tablets are not magic bullets and interventions to combat anemia must be seen in the context of overall quality of care for women and children. A severely anemic woman, for example, is at much greater risk during childbirth if birth care is not adequate.

Examples of large-scale programs that have not in the past led to a significant decrease in anemia prevalence include those in Indonesia (Sloan et al. 1992; Achadi 1995), India (Sood 1988; Gillespie et al. 1991), and the USA (Kim et al. 1992).

Problems in supply-side factors in many programs in the past have been so serious as to render it difficult to know the full extent of poor compliance as an ultimate obstacle to success — the tablets have just not been getting to people regularly enough for them to consume. Recently, in Bolivia, one million tablets deteriorated in storage because they were not distributed to peripheral health centres, nor was there a demand for them (Schoffelen, personal communication[7]). Reasons for drop-out from a supplementation program are more likely to be related to poor supply and availability of the tablets than to side-effects (Gillespie et al. 1991). For example, in India, the rate of beneficiary drop-out from the National Anaemia Control Programme in the mid-1980s ranged from 9% to 87% between different states with a mean of 58% (GOI 1989). Over 80% cited failure of the tablet supply as the reason while fewer than 3% cited side-effects from consumption. Irregular and interrupted supply and distribution along with poor counselling remain the major problems with compliance in India (Vir, personal communication[8]). Similarly, a recent publication from MotherCare (1997) states that "there is little evidence that noncompliance due to gastrointestinal side effects is an important reason that women are not taking the recommended number of iron–folate pills."

There is, on the other hand, some evidence that compliance has been a significant problem in current daily regimens (WHO 1990; Schultink 1996) and this may be related to undesirable side-effects (Ekstrom et al. 1996; Ridwan et al. 1996) and to poor communications (Galloway and McGuire 1991). In industrialized countries too, compliance may be poor (for example, Bonnar et al. 1969). In a study in Indonesia, of 33 women who had received iron tablets 2 months earlier, 21 claimed to have ingested them all, although stool samples suggested only 12 had in fact done so — giving a real compliance rate of 36% (Schultink et al. 1993). In another Indonesian study, 64% pregnant women in their second or third trimester had received prenatal care, of them 72% had been given tablets, of whom in turn 78% claimed to have taken them all — amounting to a self-reported operational effectiveness rate of about 35% (Thorand et al. 1994). In most situations, both coverage and compliance are likely to be similarly low.

Improving Effectiveness

Various options for improving program effectiveness are described here. These include:
* The need for improved communications on the problem of iron deficiency and the role of supplements in its prevention and control, and
* The possibilities with social marketing of more acceptable supplements, using flexible schedules and smaller doses, delivered weekly or biweekly as well as daily, for prevention as well as therapy.

Finally, there is a need for rigorous monitoring and evaluation of program processes and outcomes.

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[7]Schoffelen, E., 27 July 1996; UNICEF, Avenue Hernando Siles No. 5631, Esquina Calle 11, Obrajes, La Paz, Bolivia.

[8]Vir, S., 20 August 1996; UNICEF, New Delhi, India.

Communications and social marketing

Communications approaches have been seen to work in improving compliance (MotherCare 1993, 1997) through addressing the consequences of anemia and both the benefits and side-effects of supplementation. Programs to motivate women at the village level are probably essential for success. Before such a program is designed, the cultural and behavioral characteristics of the population must be assessed. Cultural characteristics, for example, placing more importance on the health of the infant than on the mother, may result prenatal services being more poorly used than postnatal services. Some mothers fear that the birth will be more difficult because taking supplements will enlarge the fetus. Depending on the type of culturally acceptable media — for example, radio, TV, or print — different techniques may need to be employed to gain the interest of the targeted population.

In one successful example in Thailand (Valyasevi 1988), motivation techniques were used for iron self-supplementation. A calendar was made to serve as a reminder for the subjects to mark daily after taking the pills. A written message in the calendar stated that the iron pill will make the mothers and their babies stronger and healthier as well as lowering the risks during delivery. Reassurance by midwives is particularly needed in the 1st week of supplementation.

Although the recent developments with iron preparations, dose size, and periodicity described later definitely offer some hope for improved program effectiveness, there is a need to guard against viewing these as the solution. There remains a dearth of well-documented studies of the effectiveness of different approaches to community-based education and communication and other essential human aspects of social mobilization, which will remain essential for the effectiveness and sustainability of any approach.

Flexible, community-based delivery systems

Nearly 50% of rural populations in developing countries do not have access to clinics for economic (for example, transport costs and wages foregone) or physical reasons (for example, inaccessibility of clinics), or both (World Bank 1993). Where attendance at clinics is low, flexibility is needed. Village health workers, midwives, or birth attendants may facilitate distribution and compliance. In Indramayu, Indonesia, community-based distribution of iron

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What Causes Poor Adherence or Compliance?

Individual factors

- Individuals do not perceive themselves to be "ill";
- Lack of understanding of signs or consequences of anemia;
- Forgetfulness or lack of motivation to take a daily supplement over a long period;
- Gastrointestinal side-effects, for example, nausea and epigastric pain, which are dose related;
- Unacceptable colour, taste, or other characteristic of the supplement;
- Fear that the supplement is a contraceptive; and
- Fear of an enlarged fetus and difficulties in delivery.

Programmatic factors

- Lack of supportive community and interpersonal education and counselling;
- Lack of compliance by functionaries to their work protocols; and
- Poor distribution or supply of supplements to delivery outlets, or both.

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supplements has been successfully undertaken using traditional birth attendants (TBAs) as distributors and promoters of supplements, backed up by an information, education, and communication campaign using radio spots, posters, stickers, and leaflets (Achadi 1995). Communities, if motivated, can decide themselves on the best option for distribution.

Other sectors may be good conduits for distribution. For example, the Ministry of Labour may organize distribution of tablets to plantation or factory workers, or during food-for-work programs. Supplements may be distributed to children at schools through the Ministry of Education. Opportunities for linking the distribution of iron supplements with contraceptives within broader family-planning approaches may also be explored.

Smaller doses

Gastrointestinal side-effects may be reduced or avoided by lowering the iron dose. Side-effects such as nausea and epigastric pain have been found to correlate with the iron dose (although constipation and diarrhea do not) (Solvell 1970). There is evidence that 30 mg of iron daily may be as efficacious as higher doses for certain groups (Cook et al. 1990). If side-effects are debilitating, 30–60 mg/day should be given and the dosage built up slowly, with tablets being taken during meals, even though absorption may be reduced. A lower dose would permit less frequent daily dosing — once per day rather than twice or more — which should itself improve compliance.

Intermittent (weekly or biweekly) doses

The assumption, based on animal studies (for example, Viteri et al. 1995a), is that weekly iron-plus-folic acid supplementation is safe, as efficacious as a daily regimen in controlling iron-deficiency anemia for certain population subgroups, and with fewer side effects. This has been borne out by several small-scale community trials (for example, Gross et al. 1994; Liu et al. 1994; Ridwan et al. 1996; Viteri 1996), and other trials are underway or about to be published. In another study in Indonesian preschool children, twice-weekly iron supplementation was similar in its effect to daily supplementation, using 30 mg supplements in each case (Schultink et al. 1995). Weekly supplementation is already part of national policy in Indonesia (to female factory workers) and the Philippines (to pregnant women).

The possibility that weekly dosing may be as efficacious as daily dosing for certain groups is hypothesized as being related to avoidance of the "mucosal blockage effect." Proponents of weekly dosing argue that a mucosal block may be avoided by more closely matching dose frequency to gut mucosal turnover time, which is about 5–6 days in humans. Such a mucosal blockage effect has, however, only been clearly demonstrated with very high iron doses administered to animals not humans (Fairweather-Tait et al. 1985). Isotopic data suggest that it does not occur in anemic individuals (IUNS 1997; Bothwell, personal communication[9]). One relevant early study clearly shows how the rate of iron absorption on a high daily iron dose (300 mg) administered to anemic individuals remains high as long as anemia is present, and only declines once the

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[9] Bothwell, T.H., 28 November 1996; Department of Medicine, University of Witwatersrand, 7 York Road, Parktown, Johannesburg, 2195 Republic of South Africa.

hemoglobin deficit has been corrected (Norrby 1974). Another study shows no evidence of a mucosal blockage effect among individuals with normal or low iron stores with either weekly or daily iron doses (Cook and Reddy 1995).

Trials with weekly doses have been conducted in China, Guatemala, Indonesia, Malaysia, Mali, and the USA among children, adolescent girls, and nonpregnant and pregnant women. A proposed meta-analysis of the various trials of this approach should provide more conclusive evidence of the degree of efficacy of weekly or biweekly supplementation for different groups.

An important question here is can weekly doses be effective for pregnant women? A study in China has compared the effect of weekly versus daily doses on raising hemoglobin concentrations at term among pregnant women who received supplements for more than 12 weeks (median: 21 weeks) (Liu et al. 1995). The study found that weekly supplementation with 120 mg iron was more effective than a daily 60 mg dose and almost as effective as a daily 120 mg dose, with fewer side-effects and rejections. Another study in Guatemala (Chew et al. 1996) found a weekly 180 mg iron dose to be less effective than a daily 60-mg dose. In both studies, however, the most important correlate of final hemoglobin was initial hemoglobin — once more demonstrating the paramount important of raising iron status before pregnancy.

The question of whether weekly supplementation can effectively substitute for daily supplements in pregnant women will be fully investigated by the meta-analysis. However, it is possible to consider what it would take for a weekly dose to suffice. As discussed in *Pregnancy* (page 11), the total iron requirement during pregnancy of a 55-kg woman who starts pregnancy without anemia, is about 845 mg. Such a requirement may be met through the mobilization of stores, from dietary sources, and from supplements. In most pregnant women from developing countries, there will be few if any stores to mobilize. With respect to diet, perhaps 500 mg could be derived from a daily dietary intake of 12–15 mg with 15% absorption in a diet with high bioavailability of iron. This would leave an additional 345 mg iron requirement. A 60-mg daily dose for 100 days with 10% absorption would provide 600 mg and amply cover this remaining requirement. Alternately, a weekly dose of 120 mg, assuming the absorption is double that of the daily dose (as a result of an hypothesized mucosal blockage effect), would provide about 340 mg over the same 100-day period — thus virtually meeting the remaining requirement of 345 mg. If absorption of a weekly dose is similar to that of a daily dose (that is, there is no significant mucosal block), then weekly dosing would clearly fail to meet the requirement.

Even assuming a doubled iron absorption rate, for a weekly regimen to meet the iron costs of pregnancy, the woman would need to be regularly consuming a diet with high bioavailability of iron and to fully comply with taking all weekly doses throughout at least the last trimester.

If the efficacy of weekly doses for certain subgroups is demonstrated in this meta-analysis, operational effectiveness in large-scale programmatic conditions would still need to be assessed. To what extent would the essential prerequisites for success be met by weekly as opposed to daily supplementation? Obviously, if a weekly dose of iron could be shown to have the same effect as a daily dose, the cost of iron supplies would be sharply reduced. However, distribution and logistics

would remain a problem, as would effective communication and support on the part of the program functionary (Yip 1996b). There is, moreover, no guarantee that a weekly regimen would result in better compliance than a daily one (Yip 1996b) — weekly malaria prophylaxis programs do not have good records of compliance (for example, Heymann et al. 1990). A higher weekly dose could actually reduce compliance if it led to more frequent side effects. Better opportunities may, however, exist for supervised administration of weekly doses to nonpregnant women and children (for example, in schools or clinics or at work sites, and so forth), which may ultimately improve compliance (Yip 1996b).

The debate over weekly versus daily supplementation should not overshadow the fact that the gap between the efficacy and effectiveness of either the daily or the weekly regimen is likely to be significantly greater than that between their relative efficacies. It is thus essential that the operational effectiveness of large-scale iron-supplementation programs in the real world be demonstrated before any change to the regime is vigorously promoted.

Preventive supplementation

Preventive supplementation refers to the sustained administration of iron supplements before a period of peak iron demand in the life cycle, as an additional and complementary approach to that of therapeutic supplementation. Weekly doses may be appropriate for such an objective if compliance is found to be better. To prevent iron-deficiency anemia occurring during pregnancy, adolescent girls or women of childbearing age, or both, could be supplemented (see *Nonpregnant Women and Adolescent Girls*, page 24).

It should be remembered that prevention, as an objective, need not, however, be pursued through supplementation; rather, it can be seen as providing further justification for other nontargeted approaches such as fortification or dietary modification. Indeed, the primary objective of fortification is prevention (see *Fortification*, page 44).

A preventive, community-based approach to supplementation is increasingly being proposed as a necessary complement to the existing curative, health-centre based approach (FAO/WHO 1970; Viteri 1994, 1995; Chew et al. 1996). A long-term, weekly, low-dose (60 mg iron) supplement-ation schedule has been proposed for women of childbearing age throughout the year in areas where iron deficiency is known to be a significant problem (Viteri et al. 1996). These authors suggest that, if 10% of a weekly 60-mg dose is absorbed, this extra 0.86 mg/day in addition to absorbed dietary iron (1.0–1.5 mg) should cover the requirement of over 90% normal menstruating women (Hallberg and Rossander-Hulten 1991).

Different avenues will be needed for reaching these different groups: primarily adolescent girls. Participatory assessments of feasibility should include the views of these girls themselves. New approaches should be monitored, evaluated, and documented so that others can learn from success. Schools, health clinics, youth clubs, and the media are all avenues through which such interventions could be promoted. Boys as well as girls should be involved, given the high rates of anemia found in the multicountry International Center for Research on Women study (Kurz and Johnson-Welch 1994).

Acceptability of supplements

Iron supplements often suffer from a lack of "status," and they may often disintegrate. The appropriate design of iron supplements, with regard to colour, dissolution time, stability, and packaging may lead to improved acceptability and thus effectiveness of supplementation systems. Colouring of tablets should be region specific, with cultural perceptions being taken into account — for example, white may not be an acceptable colour in many countries.

Monitoring and evaluation

There is a widespread paucity of documented evaluations of large-scale iron supplementation programs. Monitoring systems do not appear to have much priority in program design and, as a result, mistakes are perpetuated and bad programs are not improved or stopped. Without adequate documentation, little can be learned from success or failure. Data on both process and biological outcome indicators require regular collection and use in any management-information system. Those responsible for managing programs should be encouraged to document and share experiences, highlight constraints faced and remedies explored, and disseminate these findings.

Summary

In sum up, the effectiveness of supplementation programs is likely to depend primarily on the following eight factors, starting at the community level.

- **Community demand** must be based on community awareness of the problem and on the consequences of iron-deficiency anemia and the benefits from supplementation, as well as the motivation to continue taking supplements. To generate such an awareness and demand, an explicit communications component will be needed in any program: one that is aimed at both women and men. Communications need to derive from an understanding of local terms, perceptions, beliefs, traditions, and perceived obstacles to compliance, including side-effects.

- **Program functionaries** must be community-based, motivated, well-trained, approachable, and supportive. They must be able to explain the nature of the problem and how it can be tackled successfully, including through other diet-based approaches. Supplements should be promoted positively as health-promoting rather than negatively as disease-curing. Adequate supervision and performance monitoring is also required. Community leaders should also be involved as educators.

- **Population coverage** must be good and targeted to at-risk groups (for example, pregnant women and adolescent girls) and at-risk areas (for example, endemic malarial or hookworm-infested areas).

- **Supplementation** must be initiated early in pregnancy. Late initiation cannot be compensated for by higher doses (for example, 120–240 mg daily) later, which would also lead to more side-effects.

- **Delivery systems** must be of good quality and accessible to the target population. As far as possible, these should be functionally integrated within (but not necessarily limited to) existing channels, for example, schools, TBAs, through the Expanded Programme on Immunization (EPI) outreach, and so forth. Supplements could also be made available at retail stores, either free, at-cost, or in exchange for a coupon from the health centre.

- **The procurement process** must be well organized and the supply regular and timely with low-cost supplements delivered to outlets based on appropriate targeting criteria.

Food-Based Strategies

Food-based strategies are ultimately the most desirable and sustainable of all preventive strategies, with potential for multiple nutritional benefits, over the medium and long term. They largely comprise two different types:

* Dietary modification including food processing, preparation, and consumption; breastfeeding; and appropriate complementary food preparation and feeding practices. Agricultural production and extension, including selective plant breeding, may be considered as a form of macro-level dietary modification.
* Fortification of foodstuffs with added iron or enrichment to restore iron lost in food processing.

* **Supplements** must be of good quality, stability, shelf life, colour, and smell and acceptable to the local population.
* **Monitoring** must be simple but effective at all levels of the system from supplement supply, through coverage and compliance with consumption, to biological impact.

DIETARY MODIFICATION

Iron deficiency occurs when the amount of dietary iron is absorbed over extended periods is insufficient to meet body iron needs, including those imposed by pathologic causes (for example, hookworm infection). It relates both to the actual quantity of intake and to the bioavailability of a given intake. Bioavailability refers to the availability of a substance from the diet for use in normal metabolic processes and functions, and is influenced by both dietary factors (see next section, *Dietary Factors Influencing Bioavailability*) and host-related physiological factors (see *Physiological Factors Affecting Absorption*, page 36).

Dietary modification, as discussed in this section, is primarily a strategy for improving either the amount of food-iron ingested in the diet or its bioavailability. In addition, the production and availability of dietary iron at a macro level is described in a later section along with the potential for selective crop breeding to increase the iron content or its bioavailability in staple foods.

Dietary Factors Influencing Bioavailability

Normal individuals maintain iron balance almost entirely by regulating iron absorption. Absorbability of iron is influenced by the following four dietary characteristics: dietary-iron content, physicochemical form of the food, other dietary constituents, and food-processing techniques (Fairweather-Tait 1995).

Dietary-iron content

The iron dose is generally inversely related to the percentage that is absorbed, both with dietary iron and iron supplements (Hahn et al. 1951). The higher the level of iron to which the intestinal mucosal cells have been exposed, the lower is the relative efficiency of iron absorption (Norrby 1974). However, providing that the iron is in an assimilable form, the actual amount absorbed will rise progressively with increasing dietary intake (Fairweather-Tait 1995).

Physicochemical form of the food

Dietary iron exists as either heme iron (in meat, poultry, and fish) or nonheme iron (in milk, eggs, cereals, vegetables, and fruits). These two forms are absorbed by different pathways and with different degrees of efficiency. Heme iron is 20–30% absorbed in normal individuals (40–50% in iron-deficient subjects — see *Body stores*, page 36) and this process is relatively unaffected by dietary and physiological variables (FAO/WHO 1988). However, only 10–15% of dietary iron is in the heme form, even in diets where meat consumption is high. By far the main proportion of dietary iron in developing countries is in the inorganic nonheme form derived from the cereal-based diets. In China, for example, of the mean daily per caput iron intake of 11.7 mg, 10.3 mg derives from plant sources, mainly rice, wheat, and vegetables (ACC/SCN 1992).

Absorption of nonheme iron is governed by its solubility in the upper part of the small intestine (Charlton and Bothwell 1983), which in turn is highly dependent on the balance of absorption inhibitors and enhancers (see *Other dietary constituents*, next section) that exist in the diet as consumed (Hallberg 1981). Nonheme iron absorption may be as low as 5% in many cereal-based diets commonly consumed in developing countries. In fact, the balance of dietary constituents may cause the nonheme iron absorption to vary within a range of 1–40% in individuals of comparable iron status (FAO/WHO 1988).

Some nonheme iron derives from contamination during food preparation, for example, through use of iron cooking pots in fermentation or low pH environments. Contamination iron is not readily solubilized, although a significant proportion may be available for absorption (Hercberg et al. 1987; Guiro et al. 1991).

Other dietary constituents[10]

The various inhibitors and enhancers of iron absorption are listed in Table 4. Inhibitors such as phytates and polyphenols act through forming large insoluble polymers, thus decreasing the overall solubility of iron in the meal. Phytate inhibits trace mineral absorption in general, not only iron, and has been shown to be associated with stunting in young children through its contribution to zinc deficiency (Yip et al. 1996a). It is the main cause of the inhibitory action of bran on iron absorption (Hallberg et al. 1987).

Enhancers such as ascorbic acid form soluble complexes with iron preventing precipitation and polymerization. Ascorbic acid also reduces ferric iron to ferrous iron, which is better absorbed at pH values greater than 3 as found in the duodenum and small intestine. The enhancing effect of ascorbic acid is dose related and apparent even in the presence of inhibitors (Hallberg 1987). Citrate is also a major enhancer present in fruits and vegetables (Hazell and Johnson 1987). As well as being highly absorbed itself, heme iron, usually within meat, also enhances absorption of nonheme iron — possibly through formation of complexes with amino acids such as cysteine or peptides (Bezwoda et al. 1983). Both meat and alcohol promote gastric acid secretion, which lowers the pH of the stomach contents thus improving solubility and hence bioavailability of dietary iron.

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[10] An extremely comprehensive review of options for modifying dietary composition to improve iron bioavailability has recently been published by OMNI (Allen and Ahluwalia 1997).

Table 4. Dietary enhancers and inhibitors of iron absorption.

Active substance	Food examples
Absorption enhancers	
Ascorbic and citric acids	Papaya, guava, pawpaw, plums, rhubarb, banana, mango, pear, cantaloupe, cauliflower, salad, and orange, lemon, lime, pear, apple, and pineapple juices
Malic and tartaric acids	Carrots, potato, beetroot, pumpkin, broccoli, tomato, cabbage, and turnip
Cysteine-containing peptides	Beef, lamb, pork, liver, chicken, and fish
Ethanol	White wine and beer
Fermentation products	Soy sauce and sauerkraut
Absorption inhibitors	
Phytate	Wheat bran, rice, maize, soy protein, oats, milk chocolate, nuts, and legumes
Polyphenols	Tea, coffee,[a] spinach, oregano, nuts, legumes, and red wine
Calcium and phosphate	Milk and cheese

Source: Adapted from Fairweather-Tait (1995).

a   A recent study of Guatemalan toddlers who do drink coffee showed that discontinuing coffee intake only had a beneficial effect on plasma ferritin levels of those children who consume iron supplements (Dewey et al. 1997).

Nutrient interactions are also important considerations with respect to iron absorption and utilization.

*   Folate and vitamin B-12 modify iron utilization through their role in nucleic acid synthesis and red blood cell production (Velez et al. 1966).
*   Vitamin A is involved in iron-store mobilization, and poor vitamin A status has been reported as being associated with altered iron metabolism and iron-deficiency anemia (Mejia and Arroyave 1982; Suharno et al. 1993).
*   Riboflavin deficiency tends to both coexist and interact with iron deficiency (Powers 1996). A recent study has shown that even a transient depletion of riboflavin at around 6 months of age disturbs gastrointestinal development, which can reduce iron absorption (Williams et al. 1996). Improving riboflavin intake in riboflavin-deficient subjects has been shown to lead to an increase in circulating hemoglobin as well as an improved hematological response to iron supplements (Powers et al. 1983), probably predominantly because of an accelerated epithelial turnover in the small intestine (Powers et al. 1993).
*   Calcium inhibits the absorption of both heme and nonheme iron, possibly through inhibition of iron transport (Hallberg et al. 1992; Gleerup et al. 1995) although long-term

administration of calcium supplementation with meals does not adversely affect body iron stores (Minihane et al. 1997). Manganese and phosphate also inhibit iron absorption.

- Copper is involved in the oxidation and reduction of iron, which is important for its absorption, transport, storage, and mobilization (BNF 1995).
- Iron deficiency may also impair iodine utilization through its adverse effect on thyroid function and favour the absorption of lead and other heavy metals (see *Other Consequences*, page 19).
- Although iron absorption is little affected by zinc deficiency, it can be reduced by high zinc intakes (over 50 mg/day) from supplements (Yadrick et al. 1989).

Food-processing techniques
Heating has differing effects depending on the food matrix and physicochemical form of the added iron. Wet-heat processing tends to increase bioavailability, as will any enzymatic process that results in high phytase activity — for example, soaking, malting, germination, lactic acid fermentation, and leavening of bread with yeast (Svanberg 1995). Germination may increase bioavailability 2-fold and the malting of minor millets up to 5- to 10-fold (DeMaeyer 1989). Phytates may also be physically removed through extraction and dehulling of grains although this will also remove some of the iron and the net effect is limited (Brune et al. 1992).

Physiological Factors Affecting Absorption
In addition to the four dietary factors already described, the size of body iron stores, the physiological state of the individual, and other factors influence absorption, and hence bioavailability, of nonheme iron.

Body stores
The percentage absorption of dietary iron is inversely related to the level of an individual's iron stores: this is particularly marked with low body stores or in the presence of iron deficiency (Baynes et al. 1987; Cook 1990; Skikine and Baynes 1994). Women have a higher absorption efficiency than men, which is a function of their lower iron stores due to menstrual blood loss.

When body stores are as high as 500 mg (serum ferritin levels of about 50–60 µg/L) with a high or intermediate bioavailability diet (see *To What Extent Can the Diet Support Adequate Iron Nutriture?* page 37), iron absorption approximates maintenance levels (that is, matches basal losses) and is largely independent of dietary composition (Monsen et al. 1978; Hulten et al. 1995). In fact, for individuals with serum ferritin values above 25 µg/L, dietary factors play only a small role in determining absorption from foods of different absorbability (BNF 1995). As iron stores diminish, dietary composition takes on increasing importance for overall iron absorption and becomes highly significant for iron-deficient or anemic individuals. People who subsist on diets with low bioavailability of iron are at higher risk of anemia and even nonanemic individuals will have few iron reserves (Franzetti et al. 1984).

Physiological state
There is evidence of a significant increase in absorption during pregnancy (Svanberg et al. 1976; Whittaker et al. 1991; Barrett et al. 1994) that is related not only to the progression of iron demand but also to certain metabolic adaptations. A more than fivefold increase in absorption

(from 7% to 37%) was seen between the 12th and 36th week of pregnancy on a dose of 5 mg iron as ferrous sulphate (Whittaker et al. 1991).

Other physiological factors
Gastric acid secretions have been shown to be positively associated with iron absorption, whereas the rate of stomach emptying is inversely related (Bothwell et al. 1979; BNF 1995).

In sum, the degree of iron absorption from the diet is governed by the particular relationship between the iron requirements of the individual, his or her iron status, and the various constituents of the diet as consumed.

To What Extent Can the Diet Support Adequate Iron Nutriture?

Dietary iron intake is closely related to energy intake. Table 5 shows the relationship between median requirement for absorbed iron and an estimate of the median iron intake supplied by a cereal-based diet (which would supply about 7 mg iron/1,000 kcal), while Table 6 provides examples of the estimated bioavailability of iron from various types of diets, all relating to the prevention of any impairment of hemoglobin synthesis. If prevention of anemia were the objective, the expected bioavailabilities would be about 50% higher than shown in Table 6 (FAO/WHO 1988).

For adult men with high energy needs and food intakes, at the median levels, only 4.2% of dietary iron need be absorbed. Conversely, women with lower energy intake and higher iron need would have to absorb about 8% of the iron in the diet. Preschool children fall between these extremes with estimated necessary absorption levels of 6.1% and 5.5%.

On the cereal-based diet and assuming 5% absorption, the situation of preschool children would

Table 5. Relationship between daily iron requirement and dietary iron supply on a cereal-based diet.

	Children		Adults	
	1–2 years	2–6 years	Men	Women
Mean weight (kg)	11	16	65	55
Median energy requirement and assumed food intake (kcal)[a]	1,140	1,450	3,100	2,200
Derived iron intake (mg)[b]	8.0	10.2	21.7	15.4
Median requirement for absorbed iron (mg)[c]	0.49	0.56	0.91	1.25
Necessary absorption (%)	6.1	5.5	4.2	8.1

Source: Reproduced from Svanberg (1995).

a   Calculated from FAO/WHO/UNU (1985).
b   Assuming the diet provides 7 mg iron/1,000 kcal.
c   Calculated from FAO/WHO (1988).

Table 6. Examples of diets with estimated overall bioavailability.

Typical diet	Bioavailability of iron
Cereal-based, roots, or tubers, and legumes with negligible meat, fish, or ascorbic acid-rich foods	Low (5% absorption)
Cereal-based, roots or tubers with negligible quantities of food of animal origin or containing ascorbic acid (albeit higher than for the "low" diet) or a diet with still higher levels of animal source foods or ascorbic acid but also large amounts of tea or coffee consumed with meals	Intermediate (10% absorption)
Diversified diet containing generous quantities of meat, poultry, and fish or foods containing high amounts of ascorbic acid	High (15% absorption)

Source: FAO/WHO (1988).

Note: These absorption figures would be expected to increase by about 50% when the iron status is just sufficient to prevent anemia.

seem marginal at best, although perhaps adequate to prevent anemia (where the estimated absorption limit would be closer to 7.5% (FAO/WHO 1988)). Adult women would be at risk of anemia, while adult men should have an ample supply.

The FAO/WHO classification has since been further modified to estimate the bioavailability of iron from diets of preschool children in Egypt, Kenya, and Mexico (Murphy et al. 1996) with respect to their contents of heme-containing foods and ascorbic acid (Table 7). In addition, a tea factor was used, ranging from 1 if no tea was consumed to 0.40 for at least 600 mL tea per day. The final algorithm was:

available iron = heme iron × 0.25 + (nonheme iron × availability factor × tea factor)

The model did not contain a coffee factor as it was developed for young children, but this factor might range from 1 (no coffee) to 0.6 (Derman et al. 1977; Morck et al. 1983) and could be factored into the algorithm.

Table 7. Estimated percent bioavailability of nonheme iron for iron-deficient, nonanemic individuals with respect to daily intakes of meat, fish, or poultry and ascorbic acid.

Ascorbic acid (mg/1,000 kcal)	Percent bioavailability with intake of meat, fish, and poultry protein[a] of –		
	<9 g	9–27 g	>27 g
<35	5	10	15
35–105	10	15	15
>105	15	15	15

Source: Murphy et al. (1996).

a   (meat + fish + poultry protein) × 5 = weight of meat + fish + poultry.

This is obviously a rudimentary tool in that the ranges within categories are wide. Moreover, the algorithm would be limited in estimating the bioavailability in high phytate-containing diets, as no specific increments were proposed with respect to varying phytate contents. However, it does serve to illustrate the type and size of changes in bioavailability that may be expected through certain dietary modifications.

Infants

The first foods that infants consume tend not to be favourable for iron absorption. These include cereal- and pulse-based gruels, rich in iron-inhibitory phytate, and cow's milk, which contains low concentrations of iron and high levels of protein, calcium, and phosphorus that form insoluble complexes with iron in the intestine (Monsen and Cook 1976; Hurrell et al. 1989) reducing absorption (Lonnerdahl 1990). Meat is unlikely to be included in the infant's diet, whether for economic, cultural, or religious reasons, nor are infants likely to consume much iron-enhancing ascorbic acid. In such situations, infants are likely to be anemic by 1 year of age (Yip 1994).

The issue for infants is not only the type of foods that are introduced, but also when they are introduced. Delayed initiation of complementary feeding is widespread in developing countries and has serious nutritional implications with respect to stunting and iron deficiency. In India, for example, data from the 1992–93 National Family Health Survey (IIPS 1994) show that only 31% of 6- to 9-month-old children received semisolids nationally, with some states being as low as 9%. Given the high prevalence of low birth weight of India and other South Asian countries (about one-third of all newborns), the likelihood of iron-deficiency anemia developing is extremely high.

In addition, if complementary feeding is started too early, this may reduce the absorption of iron from breast milk. Such an inhibitory effect has been demonstrated in adults fed solid foods along with breast milk (Oski and Landaw 1980).

Pregnancy

The iron demands of pregnancy for women who are not iron deficient can be met only with an intermediate bioavailability diet (Barrett et al. 1994). Absorption of dietary iron may be enough to prevent the development of iron deficiency if prepregnancy iron stores are at least 300 mg — a situation that applies to only about 40% women in industrialized countries (Cook et al. 1986) and only 15–20% women in developing countries (Franzetti et al. 1984). Even with such reserves, the iron demand in the latter two trimesters (see Table 2) could hardly be achieved with a high-bioavailability diet. The fact is that the great majority of women of childbearing age with low or nonexistent iron stores will not be able to meet their requirement for iron from the type of local diets that might realistically become available through dietary modification. The increased absorption because of low body stores and pregnancy-related metabolic adaptations might lead to some women stabilizing in equilibrium with their dietary iron intake with a mild anemia (FAO/WHO 1988).

What Is The Role of Dietary Modification?

If a communications campaign succeeded in raising awareness, first, of the problem and consequences of iron-deficiency anemia and, second, of the means of reducing this risk through consuming more (and better combinations of) meat, fruits, and vegetables, to what extent could

more of these types of foods actually be acquired by households at-risk? How much of the problem is related to poor economic or physical access, and how much to a lack of awareness? Equally, within households, what guarantee is there that appropriate new foods, once acquired, will be consumed by the most needy individuals, usually women and young children, who commonly consume least in the household with respect to their nutritional requirements?

One of the biggest barriers to appropriate behavioral change is the fact that iron (and indeed other micronutrients) are "hidden." Whereas someone who does not eat enough energy will feel hungry and try and do something about it, insufficient iron intake goes undetected. The fact that there are usually no obvious visible signs of iron-deficiency anemia — just a slow slide into a generalized lethargy — represents an important obstacle to awareness-raising.

Regarding the question of affordability, iron is known to be income-elastic with low-income households being more likely to have low iron-consumption levels. Such income elasticity derives largely from the increasing affordability of meat and fish as purchasing power increases. In the Philippines, for example, people in the highest income quintile consumed three to four times the amount of meat as those in the lowest quintile (Bouis 1991). Consumption of fruits and vegetables, however, was not income elastic. In such a setting, an educational campaign should focus on improving consumption of fruits and vegetables — in dietary combinations and preparations that are appropriate for enhancing iron absorption — which might be possible without economic improvements at the household level. In India, for example, a significant increase in hemoglobin concentrations in a community trial involving 54 anemic school children has been demonstrated with 100 mg ascorbic acid supplements given at each of two main meals for 2 months (Seshadri et al. 1985). Another trial among Chinese children showed that a daily 50-mg ascorbic acid supplement was associated with an improvement in iron status after 6 weeks (Mao and Yao 1992).

Some doubt, however, has recently been thrown on the effectiveness of an approach based on promoting fruit and vegetable consumption (de Pee et al. 1996). Although, theoretically, vegetables could improve iron status in that they contain both iron as well as vitamin C and provitamin A carotenoids, most studies have focused on the effect on vitamin A status and few have even addressed iron status. A study in Indonesia (de Pee et al. 1996) and a recent review of the literature (de Pee and West 1996) suggest that the data relating vegetable consumption to iron status are inconclusive. More research is clearly a priority to evaluate such dietary approaches.

Iron-deficiency anemia is most prevalent in countries such as India where a high proportion of the population are vegetarians and would not consume meat even if it was affordable. Attempts at dietary modification through communications in these situations would need to focus on improving the ratio of absorption enhancers to inhibitors in the habitual diet. The possibility in nonvegetarian cultures exists also of promoting the introduction of meat to complementary foods, which would also provide other important nutrients — including protein, vitamin A, and zinc (Yip et al. 1996a). Little meat would be needed so the economic constraint might not be so significant, though possible contamination might be a problem.

Even in the unlikely event that poverty were not a significant constraint and more of these expensive iron-rich foods could be bought, what are the chances of their being consumed in

sufficient quantities by those who most need them, that is, women and children? There is evidence from data from the Philippines that ratios of adequacy of iron intake for mothers and adolescent girls (0.65 and 0.77, respectively) are significantly lower than those for adult men (1.05) and adolescent boys (0.91) (Bouis et al. 1994). Adequacy ratios are also likely to be low for children — a 1979 study in India found average iron intakes among 1- to 4-year-old children to be less than one-third of those of adult men, despite their requirement being about one-half that of adult men (ACC/SCN 1992).

Two sources of inadequacy exist in such situations — first, inadequate iron density of the diet to fulfil requirements of high-risk groups in the household (see Table 2) and, second, a sociocultural bias against an equitable distribution of certain iron-rich foods in the household, for example, meat. Household diets should have an iron concentration that is adequate for all household members when eaten in a sufficient quantity to meet their respective energy needs. It may be possible for local behaviours and methods of selecting, processing, combining, and consuming foods to be successfully modified, within given economic confines, so as to improve overall intake or bioavailability of iron . The first step required is to understand what foods are consumed in a locality and how they are acquired, processed, prepared, combined as a meal, and consumed. Then there is a need to consider what is amenable to modification given the particular economic and cultural confines, such as meal composition, timing of consumption of certain foods, or preparation practices. In many cases, certain beneficial practices have died out — for example, germination and malting of cereals — and it might be important to consider why this happened and what the prospects are for reintroduced them. Approaches for obtaining relevant dietary information have been developed for vitamin A deficiency and may be effectively adapted for iron (see, for example, Underwood et al. 1989; Rosen 1992; WHO/UNICEF/UNU 1996).

The main behavioral actions to improve dietary iron adequacy would include the following five steps.
- Children should be exclusively breastfed for the first 4–6 months of life, followed by initiation of complementary feeding with foods that are iron-rich and bioavailable in appropriate preparations combined with sustained breastfeeding for the first 2 years of life.
- Intake should be increased of absorption enhancers, for example, heme iron from meat (if economically and culturally acceptable), animal protein (meat and fish), and ascorbic and citric acids from fresh fruit and vegetables. Heat destruction of vitamin C on cooking needs to be borne in mind. Some fruits and vegetables may be consumed raw, although this may not be advisable where there are problems of sanitation and food contamination.
- Intake should be reduced of inhibitors, for example, polyphenols (in legumes, tea, and coffee), phytates (in some cereals), and calcium (in milk) during meals that contribute a major part of the daily iron intake.
- Germination, malting, and fermentation should be promoted as this may enhance iron absorption by lowering the phytic acid content and possibly by producing organic acids.
- Adequate intake must be ensured of other complementary nutrients involved in iron absorption and metabolism, particularly vitamin A, folate, riboflavin, and vitamin B-12. Animal products are the best sources of these nutrients, except folate, which is available in green leafy vegetables and some fruits.

What is the Experience with Approaches to Dietary Modification?

Although many nutrition-related communications projects have been implemented during the last decade or so, generally little emphasis has been placed on evaluating their impact, and there are few clearly documented examples of successful approaches to dietary modification through behavioral change.

Evaluating impact is difficult. First, effects of behavioral change (usually increased consumption of certain types of foods) have in the past been difficult to attribute conclusively to projects — largely because of the tendency of mass media-based strategies to "pollute" the control group. Second, consumption is difficult to measure, and often relies on reported intakes, which may be inaccurate.

One exception, from an industrialized country, is the evaluation of the Women, Infant, and Children (WIC) project in the USA (Rush et al. 1988) that examined, among other outcomes, total iron intake, the contribution of WIC foods to that intake, and the hemoglobin levels in pregnant women and under-5-year-old children. The evaluation succeeded in demonstrating beneficial effects that were attributable to the combination of education and food distribution.

In northeast Thailand, significant increases in consumption of vitamin A-rich ivy gourd, as well as increased knowledge and attitudinal change resulted from a well-monitored and evaluated communications intervention (Smitasiri et al. 1993). The greatest effect occurred with mothers of 24- to 72-month-old children, while after 3 years there were significant increases in dietary vitamin A and fat intakes of pregnant and lactating women and a decrease in reported night blindness.

Economic and cultural constraints do need to be understood and addressed. In Bangladesh, a communications intervention to improve the diets of lactating women failed, because an extra 21% of the local daily wage would have been needed and women knew that, to increase their own share of food, cultural norms required that they would also have to increase the amount given to others in the family (Brown et al. 1994). As well as economic resources and information, time is a crucial concern: changes in practices that involve a greater demand on a person's time are unlikely to be adopted.

In general, where communications projects have successfully led to dietary modification, sustaining such behavioral change has been more difficult to achieve (Gillespie and Mason 1994). There may be little disincentive to reverting to original practices in the case of dietary change — nothing drastic or immediately discernible would happen. This points to the need for more positive reinforcement through regular and sustained interpersonal and mass-media communications. A strong component of an interpersonal communication project requires a reliable preexisting cadre of community-based health workers or another network of potential communicators (Favin and Griffiths 1991). Training of community-based workers (of several sectors, not just health) should incorporate approaches to counselling and participatory information, education, and communication aimed at increasing and diversifying dietary intake. This would require an understanding of local cultural traditions and taboos and appropriate support and feedback throughout the process of change.

Approaches to behavioral change should be participatory. UNICEF's "triple A" process (UNICEF 1990) — problem **assessment**, causal and resource **analysis**, followed by appropriate **action** and then reassessment — puts the "beneficiary" in the driving seat of change. External facilitators can fuel this process through support, reinforcement, and feedback. People will change their practices when convinced that there is a benefit in so doing, that these practices can be changed, and when they have the wherewithal to do so. New or extra foods would need to be available, affordable, and acceptable.

Overriding all, a real need remains for prioritizing simple, effective systems of monitoring and evaluating large-scale communications approaches in the developing world to see what can be achieved under what conditions and through what processes. Without the ability to demonstrate effect, it is difficult to see how long-term political support at any level can be effectively harnessed for dietary-modification approaches. A participatory management-information system, including a few key indicators of process and outcome, should be an essential component of all future dietary-modification programs.

Despite some of the shortcomings identified here, including the lack of information on effectiveness, behavioral change is likely to be fundamental to the long-term success of many of the interventions discussed in this paper. In addition to food consumption, behaviour with respect to taking iron supplements, for example, will be crucial (see *Supplementation*, page 22). Dietary modification also has the potential for improving the consumption of other micronutrients that may be lacking in the habitual diet.

Agriculture and Crop Breeding

Regarding overall availability of dietary iron, the per-caput dietary supply as estimated from FAO data appears to be static or even declining in all regions except the Near East and North Africa and is particularly limiting in sub-Saharan Africa, South Asia, and South-East Asia, the regions with the highest prevalences of anemia (ACC/SCN 1992). The decline in Asia may be related to the shift away from pulses to wheat and rice for which "green revolution" technologies are applicable, whereas in sub-Saharan Africa, millet and sorghum production is on the decline. Iron density, which was already low in the predominantly vegetarian Indian diet, is further declining as the price of pulses — the main staple iron source for the poor — rises as production drops. A "brown revolution" may now be needed.

In theory, selective plant breeding or genetic engineering could raise the iron (and other micronutrient) content, or their bioavailability, of staple foods such as rice, wheat, or maize — a form of fortification at source. Phytate content, in particular, may be reduced (Pen et al. 1993), although the phosphorus in phytates is important for pest resistance, and the extent to which phytates can be reduced without compromising such resistance is not known. Screening for quality of such amino acids as methionine and cysteine, which may enhance iron and zinc bioavailability, might be appropriate. Another option might be for plant breeders to select for iron-efficient genotypes that allow plant roots to tap the otherwise unavailable iron in the soil.

Breeding for improving crop iron density could be a future food-based route to improve iron status for areas of subsistence farming that might be beyond the market reach of fortified foods.

While international research organizations are considering this option now (Graham and Welch 1996), it remains to be seen what can be achieved. If, in addition to improved iron density or bioavailability, the breeding also raised crop yields or disease resistance, this would provide a further incentive to adoption (Yip 1996c). Other important factors to consider include storage life, processing quality and consumer acceptability. Although the potential exists, this option is very long term and there is a need to consider what the probability of success of breeding for an iron-dense crop variety actually is, how long would it take, how much would it cost, and who would pay initially. If successful, will the iron-dense genotype be sufficiently high-yielding to facilitate adoption, and will the food product be acceptable and of good iron bioavailability?

FORTIFICATION

Fortification refers to the addition to a foodstuff of nutrients that may or may not be present naturally in the food and so improve its overall nutritional quality. Enrichment, or restoration, on the other hand, generally refers to the process of restoring nutrients that have been lost in the processing of a food.

The primary objective of iron fortification of foods is to prevent iron deficiency or sustain adequate iron status of a population over the medium to long term. Many important publications have covered the rapidly evolving subject of iron fortification in far greater detail than is done here (for example, Cook and Reusser 1983; Hurrell and Cook 1990; Bauernfeind and Lachance 1991; Clydesdale and Wierner 1985; Hurrell 1992; Blum 1995; Lotfi et al. 1996). This section is intended to highlight the key role of fortification in iron-deficiency prevention and identify the key current issues to furthering its development in countries where it is most needed.

Fortification of a foodstuff with iron makes sense only if iron deficiency is related to low iron intake, low iron bioavailability, or both (and not, for example, parasites), thus the etiology of the iron deficiency must be determined beforehand (see *Assessing Iron Status*, page 7). If successful, fortification can, over time, facilitate a rightward shift in a population's distribution of iron status that would result in lower proportions slipping from iron deficiency into frank anemia. If fortification and supplementation are undertaken concurrently in an area, then the prevalence of iron-deficiency anemia may be reduced faster than would be possible with supplementation alone.

A distinction needs to be made between fortification directed to certain segments of the population (targeted) and that directed to the entire population (general or universal). The most common targeted fortification is that of infant complementary foods described later. Other examples include hemoglobin-fortified cookies targeted to school children in Chile and fortified curry powder targeted to the Indian population living in South Africa.

It is technically more difficult to fortify foods with iron than with iodine or vitamin A because of the difficulty in finding an iron source that is bioavailable yet does not overly react with the food vehicle leading to adverse changes (Mannar 1991). Fortification tends to be especially difficult to initiate in developing countries because of a low bioavailability of dietary iron and relatively few food items being centrally processed and conforming to all the prerequisites listed in the next

section, *Food Vehicle*. There are, in addition to technical factors, important operational and financial prerequisites for effective fortification. Nevertheless, if these can be addressed and fortification successfully established, it is likely to be one of the most cost-effective and sustainable ways of improving the iron status of a population in the long run.

In this section, the main technological prerequisites for effective fortification, including an appropriate iron fortificant and an appropriate food vehicle, are discussed before considering what is known of the efficacy of small-scale fortification trials for improving the iron status of populations. The safety of iron fortification is then considered before focusing on the essential political, economic, and organizational considerations that will ultimately determine the development of an effective fortification program.

Food Vehicle

A suitable food vehicle is one that meets the following criteria with regard to the food consumption practices of the target population and its own production and marketing characteristics.

- It can be made available to the target or total population through an effective distribution system. To the extent that different foods are consumed by different target groups (particularly young children and women), there will be a need for fortifying different foods and ensuring their availability through whatever distribution channel is appropriate for that group. As well as economic access (purchasing power), physical access to at-risk groups through delivery channels needs to be ensured.
- The food is acceptable, affordable, and frequently consumed by the target or total population in fairly constant or predictable amounts (ideally proportional to energy intake), thus allowing calculation of required fortification levels. The food should ideally be consumed at each meal as absorption varies inversely with the iron content of the meal. In targeted fortification, the food vehicle should be consumed by individuals in the target group (with as little between-person variation as possible) and not consumed by persons in nontarget groups.
- The food is produced or processed (ideally centrally) in a site where the requisite technology and quality control can be applied.
- It is technologically and economically fortifiable. The marginal extra cost if any should be such that the fortified food remains within economic reach of the poorest groups who are likely to be most at risk of iron-deficiency anemia.
- It will not change in taste, texture, appearance, or colour on addition of fortificant and the vehicle should have minimal negative effect on iron absorption. There should be minimal detrimental reactions between the fortificant and other added fortificants or endogenous nutrients in the food. Dark-coloured or strong-tasting foods have an advantage as any changes can be masked, thus permitting the use of more bioavailable iron fortificants, which will also be more reactive.
- The food will not lose the iron fortificant nor will the iron segregate on subsequent processing, cooking, mixing, or storage.

Examples of foods fortified with iron include processed cereals (such as wheat, corn, and rice), salt, sugar, cookies, curry powder, fish sauce, and soy sauce. These foods are fortified according

to the standards and principles defined by bodies such as FAO/WHO (1981), the European Society for Paediatric Gasterenterology and Nutrition Committee on Nutrition (ESPGAN 1982), and the National Research Council (NRC 1989). Ultimately, for fortification to be effective on a large scale, it must be supported by national-level quality control, legislation, and regulation (see *Political, Economic, and Organizational Considerations*, page 52).

Food vehicles that are not suitable include soft drinks because more than 2–3 L/day may be consumed, which could exceed the maximum recommended daily intake of iron. Where consumption of a food varies significantly in this way, it should not form the basis of a fortification program. Fat-based foods also, including fresh dairy products, are not suitable as iron catalyzes fat oxidation, making the food rancid.

Cereals
Cereals are appropriate vehicles for fortification as they represent staple foods providing large parts of daily energy consumption in many countries. They are consumed in relatively constant amounts by all with only small day-to-day variations in the amount consumed and are often centrally processed. Wheat flour represents perhaps the most appropriate vehicle for fortification because it meets the classical considerations for food-vehicle choice. In many countries with iron deficiency, wheat flour is:

- Widely consumed in the form of bread and is affordable to groups vulnerable to iron-deficiency anaemia;
- Generally processed from whole wheat at only a few large mills in most countries — with a few exceptions where there are numerous small-scale flour producers;
- Distributed through widespread networks that reach all regions of any given country;
- Not subject to change in colour, taste, or appearance by an appropriate fortificant;
- Not subject to nutrient loss on further processing into bread or cooking; and
- Consumed in fairly constant amounts so that fortification levels can be calculated accurately (250–280 g/day: 80% white flour and 20% brown flour).

In its natural state, wheat is a good source of vitamins B1 (thiamine), B2 (riboflavin), niacin, B6 (pyridoxine), and E as well as iron and zinc. However, because most of these nutrients are concentrated in the outer layers of the wheat grain, a significant proportion is lost during the milling process. The lower the extraction rate of the flour (that is, the more the refining), the greater is the loss of vitamins and minerals.

In developed countries, fortification is designed mainly to restore the large proportion of iron lost in milling. Wheat flour is generally fortified with vitamins B1 and B2, niacin, and iron. In some countries, calcium and folate are also added. Vitamins A and D can also be added to flour.

The technology of flour fortification is simple. A premix of the micronutrients to be added is prepared or procured. The premix is then added to the flour at a uniform rate through a volumetric screw feeder located toward the end of the milling process. The premix can be fed directly onto the flour by gravity or by air convection using a pneumatic system.

Although the majority of the world's anemic people live in areas where rice is the main staple, there is still no large-scale rice fortification program, but trials have been undertaken in Papua New Guinea and the Philippines. Some of the many essential criteria for suitability mentioned

earlier cannot be fulfilled — for example, there are often numerous small-scale millers, for whom the issues of cost and technology are particularly important.

There remains a need to find a way of fortifying rice with iron that is acceptable, resists the effects of washing and cooking, yet still disintegrates in the intestinal tract. A major problem is that rice masks fortification poorly, because just a few discoloured grains may make the product unacceptable. Attempts to coat a small percentage of rice grains with ferrous sulphate and dust this with talc to mask discolouration have not been very successful. Other possibilities include the synthesis of micronutrient-rich grains from broken rice, though this leaves a grey product. Recently, in the Philippines, bioavailability studies and clinical and field trials have shown some degree of efficacy of iron-fortified rice based on a premix coated with an alcoholic suspension of ferrous sulphate (Florentino and Pedro 1996).

Salt

The technology for iron-fortifying salt has been available for the last two decades. The experience with iodizing salt is instructive here, although it is technically more difficult to fortify salt with iron than with iodine. However, salt is used for preservation, which may lead to adverse interactions, for example, when curing vegetables or cheese.

Studies in India have shown that fortification of salt is technically feasible and that salt is one of the few dietary items that is centrally processed. Commercially produced iron-fortified salt has been used in the midday meals of a school-feeding program in Tamil Nadu.

The Micronutrients Initiative with the University of Toronto is developing a stable formulation of double-fortified salt with iron (ferrous fumarate) and iodine (potassium iodide) in which dextrin encapsulates the iodine, forming a physical barrier that prevents it from interacting with water or iron. Bioavailability is not affected by such encapsulation, and the formulation is reported as having acceptable taste, colour, and stability (Diosady 1996). In vitro and in vivo bioavailability trials in humans followed by community trials to test efficacy in Ghana are being undertaken. India is considering initiating a program of double fortified salt (Rao 1994) and has recently successfully demonstrated large-scale production of an acceptable product at factory level using a dry-mixing process (Ranganathan et al. 1996).

Sugar

Sugar is an obvious option in the Caribbean and Central American countries where it is produced, although its consumption by poorest groups would need to be verified in advance. Also, it should be remembered that its potential would be diminished if it was mainly consumed in tea which has a high concentration of inhibitory polyphenols. Refined sugar has been successfully fortified with iron–EDTA (ethylenedianibetetraacetic acid) in Guatemala leading to improvements in iron status demonstrated in a 3-year trial (Viteri et al. 1981). Iron and vitamin A are compatible double-fortificants of sugar (Arroyave et al. 1979) and a program is under consideration in Guatemala (Viteri et al. 1995b).

The relatively high quantity of iron needed for fortification may be a problem when fortifying salt or sugar, as they are both hygroscopic, and iron may causes colour change and nutrient interactions in a moist environment.

Condiments

In Thailand, iron–EDTA fortification of fish-based condiments has shown promise (Garby and Areekul 1974), and fish sauce and paste have also been used in the Philippines. Iron–EDTA fortification of curry powder has been found to be effective when targeted to an Indian population in South Africa that was found to have high rates of iron-deficiency anemia. The combination of bioavailable iron–EDTA and curry powder, which enhances iron absorption through its capacity to stimulate gastric acid secretion, resulted in a very effective product (Ballot et al. 1989).

Iron Fortificant

The iron source or fortificant needs to be bioavailable, safe, affordable, stable, and compatible (not chemically reactive) with suitable food vehicles while conforming to existing regulations, as well as being of proven efficacy.

Bioavailability and safety are the two most important nutritional criteria for choosing the iron source. Most kinds of iron used for fortification are only partly soluble thus limiting bioavailability. The fraction that does dissolve will enter the nonheme iron pool and its absorption will be governed by the same mechanism as nonheme iron from other sources. Bioavailability of a nonheme fortificant is adversely affected by iron inhibitors such as tannins and phytate but increased by absorption-promoters such as ascorbic acid (see *Other dietary constituents*, page 34), so it needs to be considered in tandem with the food vehicle.

Safety relates to quantities added, expected intake, purity, and lack of interaction with other food constituents. Fortificants listed as GRAS (generally recognized as safe) by the US Food and Drug Administration (FDA) include elemental iron, ferric phosphate, ferric pyrophosphate, ferric-sodium-pyrophosphate, ferrous gluconate, ferrous lactate, and ferrous sulphate (FDA 1994).

The selection of an iron source often entails a compromise between the use of inert compounds that are poorly absorbed, and chemically reactive forms with high bioavailability, although sodium–iron–EDTA is one prominent exception to this. The following are the main groups of iron fortificants.

- Ferrous sulphate and ferrous gluconate are highly water-soluble salts with very high bioavailability yet they are also most likely to affect the stability, colour, and odour of foods. They tend to be used to fortify liquids such as milk or water.
- Ferrous fumarate, saccharate, and succinate are poorly water-soluble, less reactive, and more expensive and may be used to fortify infant cereals.
- Ferric salts, such as ferric pyrophosphate, and elemental iron in its different forms (reduced, carbonyl, and electrolytic) are water-insoluble, more inert, and less bioavailable forms of iron.
- Sodium–iron–EDTA and disodium–EDTA plus ferrous sulphate are iron chelates that have been used successfully as iron fortificants (INACG 1993), although they are fairly expensive to produce.

As stated in the recent OMNI review of dietary iron bioavailability (Allen and Ahluwalia 1997):

Assuming that the native iron content of diets in some developing countries is relatively high, that the diets are high in inhibitors, and that the iron fortificants are as poorly absorbed as the

native iron, it would probably be more effective to find sustainable approaches to improve the absorption of native iron than it would be to add fortificant iron. Alternatively, the bioavailability of the fortificant iron needs to be better than that of ferrous sulphate if it is to be consumed with diets containing substantial amounts of inhibitors.

Iron–EDTA is one such example. It is both highly soluble and chemically stable and particularly suitable for foods that require long storage or high-temperature processing. It can double bioavailability of dietary iron in high-phytate diets through reducing the inhibitory effect of both wheat phytate and high bread-baking temperatures and it causes neither nutrient interactions nor deleterious effects to the consumer (INACG 1993). Iron–EDTA is flavourless and nearly white. As with other approved fortificants, its absorption is regulated by the iron status of the recipient and thus poses no threat of chronic iron overload.

Although currently non-GRAS, largely because of concern about possible purity, sodium–iron–EDTA has been shown to be safe from toxicological studies, human absorption tests, and field fortification trials (INACG 1993). A review of the level of exposure to EDTA — one source of major concern in the USA — has shown that this is much lower than previously assumed (Whittaker et al. 1993). Moreover, unlike industrialized countries, EDTA exposure in developing countries without major food-processing industries will not be significant from any sources other than that added with iron. Iron–EDTA has been provisionally approved by the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO 1993) as safe for programmatic use at a level of 2.5 mg/kg body weight per day where iron deficiency is endemic.

The concern that iron–EDTA, a strong metal chelator, may inhibit bioavailability of other minerals such as zinc, copper, and calcium has been allayed by recent studies (Hurrell et al. 1994). Zinc absorption and retention may actually be improved in some low bioavailability diets by iron–EDTA (Davidsson et al. 1994; Hurrell et al. 1994). There is now a need for food-grade iron–EDTA to become more widely commercially available and affordable. The cost may decrease with increased demand but initially some subsidization may be required. However, cost-effectiveness or "cost per bioavailable iron" rather than cost per se should really be considered in any comparison. Although the unit cost of iron–EDTA is higher than other fortificants, so is its unit effect.

Iron Absorption and Efficacy Trials

Many studies have examined the degree of absorption of iron from fortified foods, although most of these have been done in developed countries with iron-replete populations where it has been difficult to demonstrate efficacy (Cook and Reusser 1983). Efficacy has, however, been demonstrated with wheat flour fortification in Chile (Walter et al. 1993) and with iron-fortified complementary foods for infants in the USA and elsewhere (Stekel et al. 1986; Yip et al. 1987; Walter et al. 1990).

Unlike iodine or vitamin A, a realistic level of iron fortificant in a single food vehicle could only provide 20–40% of a person's iron requirement based on expected consumption (Yip 1996c). In the USA, wheat flour was fortified to a level of 44 mg iron/kg flour, providing about 25% of dietary iron intake (Raper et al. 1984). In Sweden, iron fortification of wheat flour started in the late 1940s, with iron-fortificant levels that were higher than anywhere else (65 mg/kg), providing

42% of dietary iron intake (Westin 1975). However, studies have since shown that only about 15% of this carbonyl iron actually joins the nonheme iron pool and becomes potentially available (Hallberg et al. 1986). Epidemiological evidence does exist to suggest that such fortification played a significant role in the reduction of anemia among Swedish women in the 1970s (Hallberg 1982), and recent studies have shown that the per-caput daily intake of absorbed iron in Sweden has decreased by 12% since iron fortification ceased (Olsson, personal communication[11]).

General fortification

With general (untargeted) fortification, the effect on iron-deficiency outcomes has been demonstrated in several trials in developing countries. These notably include sugar fortified with sodium–iron–EDTA and vitamin A in Guatemala (Viteri et al. 1995b), maize flour fortified with ferrous gluconate in Venezuela (Layrisse et al. 1996), curry powder fortified with sodium–iron–EDTA in South Africa (Ballot et al. 1989), salt fortified with iron in India (Narasinga Rao and Vijayasarathy 1975), and fish sauce fortified with sodium–iron–EDTA in Thailand (Garby and Areekul 1974).

These studies showed that iron intake can increase significantly beyond what could be realistically achieved by dietary modification, and that this is effective even though absorption is tied to that of the nonheme iron pool. Improvements in outcome indicators tended to occur quite quickly initially before slowing into a steady longer-term improvement of iron stores and iron status. Iron–EDTA was seen as effective in all trials in which it was studied.

Targeted fortification for infants and young children

As earlier mentioned, breast milk alone will not suffice to meet the infant's iron requirements after 4–6 months, and the possibility of fortifying complementary foods for children from this age should be explored where iron deficiency is common. This is the most common form of targeted fortification, for which a clear effect has been shown (INACG 1986; Rush et al. 1988).

The importance of iron-fortified infant foods is borne out by the fact that in countries that do not fortify infant foods or before such foods were fortified, anemia among infants, unlike adults, remained quite high (Chan-Yip and Gary-Donald 1978; Calvo and Ginazzo 1990).

Cereal-based foods may be fortified with reduced iron of small particle size, ferrous fumarate, or ferrous succinate, while milk-based foods may be fortified with ferrous sulphate. The inhibitory effect of phytate in high extraction-rate cereal-based foods may be counteracted by adding ascorbic acid (although this is costly) or exogenous phytase to degrade the phytate (Davidsson 1996). Also, ways of increasing riboflavin content of fortified foods should be sought given the interaction between iron and riboflavin deficiencies (Powers 1996) (see *Other dietary constituents*, page 34). Iron fortification of complementary food has been found not to reduce zinc absorption (Fairweather-Tait et al. 1995).

Two trials in Chile and one in South Africa are among the few that have clearly demonstrated the efficacy of fortification in reducing anemia prevalence. In one, anemia prevalence among 3- to

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[11]Olsson, S., 12 January 1997; Department of Medicine, Oestersund Hospital, S-831 01 Oestersund, Sweden.

15-month-old children supplemented with iron-fortified milk dropped significantly, and the inclusion of vitamin C in another group was associated with a decline from 28% to 2% (Stekel et al. 1986). In another trial, the fortification of cookies with hemoglobin, derived from blood from slaughter houses and processed in a satisfactory manner, was successfully used in school-feeding programs (Stekel et al. 1986). However, sanitation concerns with blood may preclude the wider use of such fortificants, as might the ethical problems of using a fortificant that cannot be consumed by certain religious groups. Finally, a recent South African study showed a significant effect of iron-fortified soup (0.9 mg absorbable iron per school day) on the iron status of 6- to 8-year-old children after 5 months (Kruger et al. 1996).

Safety of Iron Fortification

Concern has been expressed in some quarters that food fortification, particularly if untargeted, might precipitate iron overload among certain susceptible individuals. The evidence relating to this risk has recently been reviewed (*Annex II*, page 74). Studies linking iron status to hereditary hemochromatosis, iron-loading anemias, sub-Saharan iron overload, and transfusion-dependent overload conditions are described, along with the relationships posited between iron status and the risk of cancer and coronary heart disease.

In brief, the review concluded that:

- Iron fortification will not lead to the development of iron overload among normal individuals because there is a very efficient system of down-regulation of dietary iron absorption, and an actual blocking at certain iron-store thresholds. This applies to diets with high iron bioavailabilities, high heme-iron content, and iron fortification.
- There are several genetic conditions that predispose to risk of iron overload. The risk has been found to be related to homozygosity of a defective gene. Individuals who are homozygous have been found to be a small minority among populations of European extraction, largely concentrated in "genetic hot spots," and not evenly distributed throughout the population. Heterozygotes, who are more numerous, are not at risk of iron overload. There are few data on the prevalence of hemoglobinopathies in developing-country populations.
- The amount of iron added to the diet through fortification could make a significant rightward shift in the iron-status distribution of an iron-deficient population. Fewer people would become anemic. However, such amounts would make little or no difference to the outcome for those with various hemoglobinopathies, or indeed to those individuals who develop sub-Saharan iron overload. The latter is a unique case and related to a dose that could be considered therapeutic and far above what might be provided by fortification. In addition, it is thought likely that this latter form of overload is also genetically mediated.

A recent review in the USA has concluded that food fortification with iron does not significantly increase the prevalence of overload, or the rate at which it develops, and that withdrawal of iron-fortified foods plays no role in its management (Gable 1992; Bothwell 1996; Yip et al. 1996a). Decades after Sweden embarked on an iron-fortification program (since ceased), no noticeable increase had been found at a national level in the incidence of iron overload (Lindmark and Eriksson 1985; Hallberg et al. 1989). These are populations where the iron status is considerably higher than in most developing-country populations.

A rare clinical problem in a small minority of individuals should not, in any case, be addressed with a public-health approach — in this case, withholding iron supplementation or fortification programs from the population at large. The proper approach in industrialized countries to management is a clinical one, based on case-finding through screening using biochemical tests. In developing countries, where such an approach may not be feasible, process and outcome monitoring will remain of paramount importance. There has always been a need to monitor iron concentrations in fortified foods, from the premix to the final product, and this should be combined with monitoring the effect on population iron status. This will be particularly important in malaria-endemic populations and those with sickle-cell trait (see *Malaria*, page 57).

The evidence relating iron status and risk of coronary heart disease and cancer remains controversial. Even if an association with high iron stores was found to exist in future, this would not be a contraindication for programs to prevent or control iron-deficiency anemia in developing-country populations where iron status is at the other end of the spectrum.

Political, Economic, and Organizational Considerations

In addition to the choice of food vehicle and iron source, there are other operational prerequisites that relate to relationships between public and private sectors, legislation, financial support, incentives, and management-information systems. Commitment and active collaboration between many sectors, both public and private, will be critical to getting a fortification program off the ground. Government sectors, private industry, the scientific community, media, nongovernmental organizations, consumer groups, and donors are all likely to have important roles to play and responsibilities to fulfill. A steering group comprising representatives from these sectors should be formed early on in this process to oversee the development of a fortification program.

An overall strategy for control of iron-deficiency anemia — and the place of fortification within it — should derive from an understanding of the nature, extent, and severity of iron-deficiency anemia and its causes, as far a possible. If the problem is found to be related to low dietary intake or low bioavailability of iron, or both, then fortification is an option, and a feasibility study should be undertaken. If the various technological prerequisites for fortification relating to the vehicle and fortificant are then found by industrial sector research and development to apply, and operational and financial feasibility is felt to exist, then fortification should be pursued. Linkages would then need to be developed with other intervention strategies, such as dietary modification, to exploit complementarities, particularly with respect to communications and education. The strategy would also need to address "who does what" with respect to production, distribution, budgeting, and sources of financial and technical support, management structures, and enforcement mechanisms — including incentives and legal sanctions. Disruptions to existing systems of production and distribution should be minimized. The means of monitoring at all levels — from industrial compliance with regulations, to iron concentrations in the product throughout the distribution chain, right down to the ultimate outcome of reduced prevalence of iron-deficiency anemia — would need to be clearly articulated in the strategy. A specific component of training for assessment, quality control, and monitoring would be required, along with a time-bound work plan for strategy implementation — decided and agreed upon by all actors.

Of primary concern when considering fortification as an option will be a country's food-regulatory system, including regulations governing the origin and application of food additives as

well as import and tariff regulations concerning imported compounds. In such cases, governments of countries where fortificants are to be developed and to be used should be brought into discussion early to ensure compliance with regulations during product development.

Mandatory fortification

There is a need to distinguish between voluntary and mandatory fortification. Voluntary fortification is unlikely to work in countries where consumer demand is weak, which are also those in which anemia tends to be most prevalent (World Bank 1994). It also requires a developed food industry and a certain comparative advantage for fortification as an incentive. Consumers generally cannot detect the lack of beneficial constituents in their habitual diet and are often not sufficiently aware of the consequences to demand their inclusion in fortified foods. Furthermore, there is a possible economical disincentive to voluntary fortification for pioneering companies that act first, because such companies would need to carry out expensive start-up product development, market research, and advertising. If this expense is recouped in raised prices for the fortified product, then market share may fall without consumer demand. If not, then profits will be cut. Either way, companies may prefer to wait until someone else has tested the product and market — a situation that is not conducive to overall progress.

This situation could be avoided if a government were to mandate fortification: although mandated fortification needs to be backed by a real political will. Globally, most successful fortification programs have been mandatory (World Bank 1994). Mandatory fortification does not require changes in the customary diet, nor is individual compliance, as such, an issue. It will be required in most developing countries until sufficient consumer demand and power is built up.

The legislation should seek to empower the appropriate ministry to regulate fortification of suitable foods at adequate and safe levels by establishing and enforcing specifications and directives for industrial compliance. Although the Health Ministry would probably spearhead the move toward fortification and provide the health and nutritional basis for such directives, it might not be best at performing such a regulatory role, which might better be done by the Industry Ministry, for example. The Health Ministry might be responsible for outcome monitoring (that is, availability of fortified food at market outlets and anemia prevalence) while the Industry Ministry could deal with the monitoring of the fortification process including fortificant levels and overall industrial compliance.

Even with mandatory fortification, fiscal and tariff incentives for the private sector will have a role, including low-interest loans for the purchase of fortification equipment, technical assistance, import subsidies, reduced tariffs and duties on fortificants, and special certification or labeling provisions (World Bank 1994). It is important to encourage the documentation of the cost–benefit of fortification interventions so as to provide evidence of effectiveness — both to support sustained support and to bolster future advocacy for other programs.

Few developing countries are actively pursuing iron fortification. In most cases, all the essential criteria above do not apply, although the main problems are generally not technical. First, there tends to be a lack of centralized sources for processing foods that would be commonly available

and consumed by the most at-risk population groups. This seems to be particularly true of the countries with the highest prevalences of iron-deficiency anemia, for example, the Indian sub-continent. Second, there is a lack of mobilization and harmonization of both the government and the food industry on the need to deal with the problem of iron-deficiency anemia in general and the potential of fortification in particular. Without a legislative mandate, this leads to inertia on the part of the food industry, which is not willing to bear the significant start-up costs of fortification.

Communications and advocacy

How can proven efficacy in a community trial be translated into effectiveness on a national scale? This is where solid advocacy and mobilization of the public ("better health at marginal cost"), the food industry ("technical feasibility and low cost"), and the government ("reduced ill health and improved human and economic development") needs to be undertaken. Vigorous advocacy based on cost-effectiveness criteria and the cost at all levels of not acting need to be emphasized, bringing all recent material on the adverse consequences of iron-deficiency anemia and on the success of fortification. Ultimately, consumers need to be aware of the benefits if a demand for fortification is to be generated.

A strong communications component is required in any fortification program to raise consumer awareness of the problem of iron-deficiency anemia and its consequences, as well as the means of addressing it. Social communication, using all available media, will be critical to success with fortification. Consumers would need to be convinced that the benefits outweigh the marginal extra cost, if any, of the fortified product. For a commonly consumed food vehicle with an inelastic consumer demand that is mandatorily fortified, the main issue to stress is this economic one, as the issue of choice (that is, fortified versus nonfortified) would not apply.

Improved communications are also needed between the public and private sectors who both have important roles to play. This was one conclusion of the Ottawa Forum on Food Fortification held in December 1995, which emphasized the need for an enabling environment to be nurtured, in which different roles are defined along with the particular opportunities for effective cooperation (MI/The Keystone Center/PAMM 1996). Both the public and private sectors should share the responsibility for quality assurance of a fortified product based on Codex Alimentarius guidelines and principles.

PARASITIC DISEASE CONTROL

Public-health measures for disease control, including helminth control, are complementary to other approaches described here and additive in their effect. Although, as far as possible, they should be initiated regardless of any proven benefit to iron status, they should be integrated with other approaches and intensified in areas where iron-deficiency anemia is strongly associated with high prevalences of hookworm or other parasites.

Two main strategies to reduce anemia prevalence through helminth control are deparasitization, in general, and the reduction in the prevalence of hookworm infestation and malaria, in particular.

Parasitic Worms

Hookworms (*Necator americanus* and *Ancyclostoma duodenale*) infect about 1 billion of the world's population. They cause intestinal blood loss by feeding on the intestinal mucosa, and the amount of blood lost is directly proportional to the number of worms infecting the host (Stoltzfus and Dreyfuss 1997).

Chronic fecal blood loss because of hookworm infestation is a significant contributor to anemia (particularly moderate and severe anemia) among certain populations (Roche and Layrisse 1966; Srinivasan et al. 1987) and can significantly limit the effect of other diet-based interventions. Hookworm infestation increases with age and prevalence rates are higher among adults than children. A hookworm infection of moderate intensity in a woman amounts to a fecal iron loss of 3.4 mg/day (Stephenson 1987). In a study in Nepal, where prevalence of hookworm infection was 78% among pregnant women, 32% of moderate to severe anemia and 29% of iron-deficiency anemia was found to be attributable to hookworm infection (Dreyfuss et al. 1996).

Schistosomiasis, and to a lesser degree trichuriasis and ascaris infestation, also can adversely affect iron status through provoking gastric or intestinal ulceration and blood loss. A strong association has been found between urinary schistosomiasis and iron status in sub-Saharan Africa (Stephenson et al. 1985, 1989a; Greenham 1978). A severe *Schistosoma haematobium* infestation can lead to a daily iron loss of 2.1 mg in a woman.

Preventive measures to break parasitic transmission may include keeping feces out of the soil — for example, through the use of pit latrines — and adequate hygiene and sanitation practices, and keeping skin from contact with the soil — for example, use of cheap footwear.

Studies on iron-deficient school children in Zanzibar, among whom infections with *Ascaris*, hookworms, and *Trichuris* were highly prevalent, have recently found that:

- There is a significant intensity-related relationship between hookworm infection and fecal blood loss, with modest infection causing significant blood loss. The prevalence of iron-deficiency anemia has been found to increase steadily as hookworm infection intensity and intestinal blood loss increase. In the context of a poor diet, as exists in Zanzibar, hookworm-related blood loss contributes dramatically to anemia. Rates of anemia among children with heavy hookworm infection were as high as 80% as compared to 49% among noninfected children. In addition, 25% of all anemia, 35% of iron-deficiency anemia, and 73% of severe anemia were found to be attributable to hookworm infection (Stoltzfus et al. 1997).
- In such contexts, hookworm control is a feasible and essential component of anemia control. Determining fecal heme is relatively simple and noninvasive and may be a useful tool for measuring the impact of hookworm-control activities (Stoltzfus et al. 1996a).
- Deworming at 6-month intervals was effective in reducing hookworm egg counts. In highly endemic areas where transmission is very high, 4-month intervals may be necessary to have a sufficient effect on the intensity of intestinal nematode infections to be likely to reduce morbidity (Albonico et al. 1995).
- In areas of intense hookworm transmission, deworming at such intervals has been found to improve the iron status of school children (Stoltzfus et al. 1996b). The control of hookworm infection will have the greatest benefit for that segment of the population with moderate or severe anemia (Stoltzfus et al. 1997). In one such situation, 4-month school-

based deworming was found to reduce the incidence of severe anemia (hemoglobin <7 g/dL) by 55% (Stoltzfus, personal communication[12]).

- Regarding the relative efficacy of different drugs in reducing hookworm infection, a single 400-mg dose of albendazole was found to be more effective than a 500-mg dose of generic mebendazole (albeit significantly more expensive being a proprietary drug). The difference attenuates after 4 months. Both drugs are similarly and highly effective against *Ascaris* and mebendazole is most effective against *Trichuris* although the cure rate was low. No difference was found in the frequency of side-effects between the two drugs (Albonico et al. 1994). The recommendation from this study was to deworm with albendazole where hookworm is the main parasite and cost is not a critical consideration, or with generic mebendazole where cost is a constraint or mixed infections are prevalent.

For schistosomiasis, the dose of the drug of choice, praziquantel, needs to be related to the weight of the subject where high prevalences of hematuria related to *S. haematobium* are found. Fully detailed guidelines for helminthic control measures, as a complement to iron supplementation, are provided in the forthcoming International Nutritional Anemia Consultative Group (INACG) publication (Stoltzfus and Dreyfuss 1997).

Deworming should be carried out among pregnant women after the first trimester, when it is safe (WHO 1994). Deworming of pregnant plantation workers in Sri Lanka has been found to significantly increase the beneficial effects of iron supplementation on hemoglobin concentration and iron status (Atukorala et al. 1994).

Deworming has also been associated with improved growth among school children (Stephenson et al. 1989b). Where this does happen, the impact on usual indicators of iron status will be attenuated because growth is costly on iron. Although the benefits will nevertheless accrue, they might thus be more difficult to measure. In another interesting study in South African 6- to 8-year-old children, the individual and combined effects of iron-fortified soup consumption and deworming on iron status and growth were investigated (Kruger et al. 1996). Individually, both interventions had a positive effect on both iron status and growth, but the effect was greatest where the two interventions were combined.

These studies reinforce the need to obtain data on prevalence and intensity of parasitic infection and, where prevalences are greater than 20%, include anthelminthic therapy in anemia-control strategies, particularly for school children and pregnant women. Periodic supervised deworming one to three times per year (depending on intensity) should be undertaken through the primary health-care and school systems. Schoolchildren are usually a priority target group, and the use of schools for such treatment may have other positive benefits including possible incentives to enrolment and retention. A means of reaching those children who enrol late, often not until 8–9 years of age, needs to be considered because they are no longer considered to be in the preschool category. Among preschool children, deworming should only be considered for those over 2 years old because, before this age, deworming is unlikely to be efficacious (Nestel 1995).

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[12]Stoltzfus, R., 16 September 1997; Center for Human Nutrition, Johns Hopkins School of Public Health, Baltimore, MD, USA.

Malaria

In an infected individual, iron is needed both by the individual and the infectious agent. The links between excess iron and malaria have been studied most frequently in this regard. Malaria increases the prevalence of anemia and worsens its severity (Brabin 1992; Kariks 1969) through two major routes. First, and most importantly, it causes a hemolytic anemia that leads to less iron in the hemoglobin mass and more sequestered in stores and, second, as with chronic infections, it is associated with some impairment in the release of iron from reticulendothelial stores.

The evidence supporting a direct effect of iron on malaria growth is weak (Peto and Thompson 1986) and the prooxidant theory of iron toxicity has been judged to fit better (BNF 1995). This suggests that the inflammatory response after malaria infection, plus the hemolysis, releases tissue iron that may exacerbate free radical damage in the tissues. The higher the iron status, the greater is the potential damage or disease severity (BNF 1995).

Iron deficiency does not protect against malaria (Snow et al. 1991), but parenteral iron is reported to increase the risk of respiratory infections and the prevalence and effects of malaria in infants (Oppenheimer et al. 1986b; Smith et al. 1989). After standard oral iron supplements were given to infants in the Gambia, fever was more frequently associated with severe malaria parasitemia (Smith et al. 1989), although these observations were not confirmed in infants in Cameroon (Chippaux et al. 1991), older children in the Gambia (Bates et al. 1987) and Papua New Guinea (Harvey et al. 1989), nor in pregnant women in the Gambia (Menendez et al. 1994). After treatment of malaria in Gambian children, iron supplementation was not associated with increased prevalence of malaria, but with a better hematological response (Boele van Hensbroek et al. 1995).

Recently, two randomized double-blind, placebo-controlled field trials from north-western Ethiopia, where malaria and iron deficiency coexist, have been reported as showing further interesting results. In one, there was a 10% excess risk of malarial morbidity in women of child-bearing age and young children after 3 months of iron supplementation. In the second, among school-aged children with mild to moderate iron deficiency, there was no increased malarial risk, again after 3 months supplementation. In both studies, however, there were highly significant improvements in hemoglobin concentration for the iron-supplemented groups (Gyorkos, personal communication[13]).

Sickle-cell disease[14] is another consideration with respect to malarial infection and iron control. Sickle-cell anemia is not very prevalent because of the high mortality during infancy of individuals

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[13]Gyorkos, T., 24 September 1997; Montreal General Hospital, 1650, avenue Cedar, Montreal, PQ, Canada H3G 1A4.

[14]Sickle-cell anemia is due to a genetic mutation that affects a base in one of the genes involved in hemoglobin production and reduces the oxygen-carrying capacity of the hemoglobin molecule leading to acute anemia. Homozygous individuals are likely to die early before adulthood. However, in heterozygotes (referred to as having "sickle-cell trait"), only about 40% of the hemoglobin is abnormal and this does not result in anemia. Such carriers of the trait are relatively protected from malaria as *Plasmodium* cannot live in red blood cells carrying the abnormal hemoglobin.

with the condition. Among pregnant women with sickle-cell trait in a randomized, double-blind, placebo-controlled trial in the Gambia (18% of that population), iron supplementation has been found to be associated with a reduced hematological response, increased frequency of placental malarial infection, and reduced birth weights on delivery (Menendez et al. 1995). Women without sickle-cell trait, on the other hand, benefited with respect to iron status and birth weights from supplementation. Finally, a randomized, double blind, placebo-controlled trial of iron or antimalarials, or both, in prophylactic oral dosages in normal and sickle-cell-trait infants has recently been completed and is currently being analyzed. The results of this and other future studies are needed before a routine recommendation is made on the use of iron supplements for infants in malaria-endemic areas.

The chief researcher in many of these recent studies has concluded that iron-deficiency control programs (either fortification or supplementation) must continue to be promoted in developing countries, but their effect on malaria should be monitored, especially in special groups of individuals such as those with sickle-cell trait (and perhaps iron-overload conditions) who may constitute a considerable proportion of the population (Menendez, personal communication[15]).

DIFFERENTIAL COSTS AND BENEFITS

Detailed cost-effectiveness and cost–benefit analyses have been attempted elsewhere (for example, Levin et al. 1993; World Bank 1994; WHO/UNICEF/UNU 1996; Viteri 1995b) and it is not intended to repeat their assumptions and findings in full here. Moreover, cost–benefit estimation is highly situation-specific so that only orders of magnitude can be compared meaningfully in such a summary. Comparisons are not intended to suggest that some of these approaches are alternatives. As discussed throughout this paper, approaches are complementary and each will have a role in different contexts.

Program interventions that have been successful in reducing anemia among adolescents and adult women have been viewed as among the most highly cost-effective nutrition and health interventions for women (Tinker et al. 1994). With a delivery cost of US$2–4 per person annually, iron supplementation of pregnant women costs just US$12.8 per DALY (disability-adjusted life year) saved. Iron fortification is one-third of this, at just US$4.4 per DALY saved. These values compare with US$9.3 and US$7.5 for vitamin A supplementation and salt iodization respectively (World Bank 1994).

The cost of supplementation includes the price of the iron tablets, the cost of its transportation and distribution to points of administration, and the cost of publicity and communications needed to ensure compliance. If administered through the existing delivery system, the main additional expense will be related to the training and orientation of staff and the time they require for supplement distribution, communication support, and compliance and effectiveness monitoring. If, however, special staff are recruited for tablet distribution, expenses will be much greater.

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[15]Menendez, C., 12 December 1996; Corporacio Sanitaria Clinic, Villaroel 170, Barcelona 08036, Spain.

UNICEF's sugar-coated ferrous sulphate tablets are the most inexpensive tablets, costing about US$1 per 1,000 tablets, as compared to open market costs of around US$4–10 per 1,000. Weekly iron-supplement administration reduces these values considerably, although it should be remembered that programmatic objectives may differ too, which would need to be accounted for when comparing cost-effectiveness.

Marginal costs involved in fortification programs include those for the fortificants, mixing, equipment, and marketing. Initial costs are modest and recurring costs less than those with supplementation. These are marginal costs that relate to the modification of an existing process; clearly costs would be much higher in the case of the de novo introduction of a processed food, such as fortified complementary food. In an analysis of the costs of fortifying foods for refugees, the major cost was found to be related to the milling of whole grain cereals, not the addition of nutrients (Beaton, personal communication[16]), which illustrates the particular need in fortification to consider how different costs in the process should be met.

In a study to compare the cost-effectiveness of iron supplementation and fortification programs, Levin et al. (1993) estimated costs for large-scale fortification programs as US$ 0.10 per person per year for salt fortification in India and sugar fortification with iron–EDTA in Guatemala. The hemoglobin fortification of cookies for children in Chile also cost US$0.10 per person per year (Stekel et al. 1986): this would be doubled if ascorbic acid was added. For supplementation with ferrous sulphate tablets, delivery costs ranged from US$ 2.70 to S$ 4.40 per person per year, depending on population density and other services provided by health workers (Levin et al. 1993).

Deworming has been estimated as costing US$0.025–0.20 per treatment (Warren et al. 1993; Nahmias et al. 1989) or US$0.16 for albendazole and US$0.74 for praziquantel in a school-based strategy in Ghana (Bundy, personal communication[17]). The requirement to target praziquantel and to adjust the dose by weight of the subject significantly increases the delivery cost.

For other approaches, such as dietary modification and communications approaches, there is a marked lack of data. Moreover, there are potentially many other benefits beyond improved iron nutriture that would need to be accounted for in a comprehensive estimation of cost-effectiveness or cost–benefit analysis.

Regarding the benefits of anemia reduction, although many are difficult or impossible to fully quantify, those accruing from increased labour productivity alone have been found to be impressive. Annual per-capita benefits (using 1980 figures) have been found to range from US$7 in Indonesia to US$43 in Kenya and US$57 in Mexico after a 10% increase in hemoglobin concentration resulting from iron fortification (Levin et al. 1993). With a 25% increase in hemoglobin concentration after supplementation, the annual per-capita benefits were about

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[16] Beaton, G.H., 12 July 1997; GHB Consulting, 9 Silverview Drive, Willowdale, ON, Canada M2M 2B2.

[17] Bundy, D., 19 December 1996; University of Oxford, Centre for Epidemiology of Infectious Disease, South Parks Road, Oxford, UK OX1 3PS.

US$18 in Indonesia, US$107 in Kenya, and US$142 in Mexico. Such productivity benefits are clearly not the only type of benefit, nor necessarily the most significant, so such figures are gross underestimates of the total benefits. Cognitive and morbidity benefits are just two examples of additional major benefits that will accrue from avoidance or mitigation of the type of consequences described earlier (see *Consequences*, page 14).

Benefits of iron-deficiency control programs have been found to lie within the range of US$6–58 yield for US$1 initial investment cost. Benefit–cost ratios, estimated under certain assumptions at 30 to 1 (Viteri 1991), are at least as favourable as those for vitamin A or salt iodization. In the worst-case scenario, financial and social benefits should outweigh costs within 3–4 years (Viteri 1991). Such programs are clearly highly productive investments for many developing countries.

SUMMARY
AND CONCLUSIONS

SUMMARY PROGRAMMING GUIDELINES

The steps to be taken in effectively initiating and implementing a program to prevent or control iron deficiency and anemia are no different in principle to any other program. The iterative, cyclical process of problem assessment, causal and resource analysis, design and implementation of a program, and reassessment of the situation should be followed. As with any other program, such steps should directly involve and empower the communities and individuals affected.

The following are summary guidelines or steps in initiating and implementing a program, but should be adapted to the particular national or large-scale situation.

Assessment
The first step is to gain some understanding of who is affected, where they are living, how many are affected, and as far as possible how severe the problem is. Although factors such as age, sex, physiologic status, socioeconomic status, geographic region, urban versus rural, and so forth are all likely to be important in differentiating groups, a first priority would be to assess the prevalence of anemia among pregnant women and 6- to 24-month-old children. Secondary clinic-based data may be checked, but this in itself is unlikely to suffice in many situations given the low utilization of health services. Impressions of women in the community should also be elicited. Rapid community-based surveys may be undertaken on a small sample of pregnant women using a HemoCue with the help of local health workers, traditional birth attendants, and so on. A sample of adult men may also be usefully included to investigate etiology (see later).

Analysis
The next step is to investigate the possible main causes of the problem. Although the main contributing factor is highly likely to be iron deficiency, other factors such as malaria, other parasitic infections, low birth spacing, and so on, may be important. Etiology may be investigated through a comparison of hemoglobin distributions of different subgroups (see *Assessing Iron Status*, page 7). If men are affected, then hookworm, malaria, or other diseases are likely to be important contributory causes.

In addition to such a causal analysis, the type and amount of resources to deal with the problem need to be analyzed. An inventory is needed of the following categories of available resources, along with an understanding of who controls their use and how they are used in practice:
- **Human resources**: This will include, for example, personnel capacity of relevant sectors and communities, training, supervision, and outreach. Also community felt needs, perceptions, attitudes, and capacity that will affect use of services and involvement in interventions must be considered.
- **Financial resources**. Costs will include personnel training and work time, supplements, communications, fortificants, technologies, and so on. Sources of finance may include governmental budget allocations as well as private sector and community contributions.
- **Organizational resources**. This would include infrastructures related to different approaches (for example, primary health care, food processing, and schools), their population coverage and accessibility, delivery systems, transport, procurement, and

storage. Community-based organizations (for example, women's groups and village committees) and potential delivery systems as well as mechanisms for intersectoral collaboration between different public sectors and between the public and private sectors are also involved.

The amount, control, and use of these three types of resources are determined in large part by political considerations such as the degree of commitment to iron-deficiency prevention and control with respect to other priorities.

The next step is to decide, on the basis of these factors, what can be achieved over what time periods. Realistic but challenging goals and specific, quantified, time-bound objectives need to be set. Both outcome and process objectives are required. One example of an outcome objective would be "the reduction of iron-deficiency anemia among pregnant women by X% in 10 years." Process objectives toward this outcome might include "achievement of certain steps toward fortifying an appropriate foodstuff," "the coverage of Y% of pregnant women with iron supplements," and "Z% compliance with the prescribed regimen within 5 years of the program's inception."

Action

There are different tiers of action with different actors. Appropriate supportive policy will be paramount for all approaches, overriding and determining the planning, design, and implement-ation of relevant programs. Throughout such processes, the active involvement of communities most affected by iron deficiency will be essential. Community participation should not just be latched onto programs in a perfunctory manner as often happens — it should form the foundation of the program and drive the processes of its design, implementation, and monitoring. As such, and for real sustainability, it is better to speak of community ownership.

Before undertaking any action, there will be a need to consider which combinations of strategies are feasible and appropriate for dealing with the identified causes of the problem in a given time frame. Each of the strategies described in this paper has certain prerequisites or criteria for appropriateness in different situations. The choice of the mix of strategies to be employed within a program will depend on the results of the assessment and analysis stages described earlier and the balance between the respective advantages and constraints of strategies in a given situation. A blanket prescription of any one approach without knowing the problem situation and ground resource realities is not realistic or desirable — hence the need to follow this "triple A" process: assessment, analysis, and action.

An expert consultation on the determinants of anemia, organized by the Micronutrient Initiative in September 1997, led to the design of a life-cycle risk matrix for use as an aid in analyzing the etiology of anemia. Such a matrix could also be used for deciding on appropriate action at each life-cycle stage.

In general, where the prevalence is higher than 30% in pregnant women, it can be assumed that anemia is a highly significant problem and will be present among a high proportion of infants and young children as well as other vulnerable groups such as adolescents. In such a situation,

universal daily iron and folic acid supplementation to all pregnant women and children aged 6–24 months should be undertaken. At the same time, preventive daily or weekly supplementation for adolescents and nonpregnant women should be considered.

Where a major cause of iron deficiency is low iron intake or poor iron bioavailability, then fortification is an option that should be pursued. A feasibility study should be undertaken to determine whether the various preconditions for effective fortification — including those relating to the food vehicle, the fortificant, and the political, economic, and organizational prerequisites — are in place. Options for improving the iron content and bioavailability of the habitually consumed diet should also be pursued through a range of media, based on good formative research on the various factors that are constraining consumption of iron-rich, iron-bioavailable foods. If malaria or hookworm are prevalent, preventive and therapeutic measures need to be taken.

The time frames for different strategies to take effect differ. Daily supplementation is short term and often corrective, whereas weekly supplementation may be considered preventive over the medium to long term. Both fortification and dietary modification are medium to long term in their effect. The development and effective marketing of a fortified product can take up to 10 years.

Time is an important consideration with regard to what happens when. For example, although supplementation may act rapidly, this does not mean that it will not be required once longer-acting strategies have taken effect. It will probably always be needed for certain groups at certain highly iron-demanding stages of the life cycle, for example, for women when pregnant. By the same token, the fact that some strategies are considered longer term in their effect should not be construed as licence to delay their implementation until more rapidly acting strategies have been put in place.

Some strategies do not need to be justified solely with respect to a population's iron status as they have other powerful objectives, for example, malaria control and infectious disease control. The serious consequences of not acting (see *Consequences*, page 14) also need to be borne in mind. For example, the educability of children is likely to be significantly improved where effective prevention and control strategies are in place in areas of high prevalence of anemia.

Certain strategies, such as fortification and dietary modification, may be so designed as to simultaneously affect other problem areas, for example, communications approaches for preventing iron and vitamin A deficiencies, double-fortification of salt, and so on. Even supplements can be combined so as to have an effect on multiple deficiencies, for example, iron and folic acid tablets now available for pregnant women and, possibly in future, iron and zinc supplements for children.

Overriding any approach, at all levels, there are three key program support activities to be employed: advocacy and communication, training and orientation of personnel, and operational or applied research.

Before program implementation, a time-bound plan of action will need to be drawn up with key roles and responsibilities of all those to be involved. As a subset of this, an "advocacy and

communication plan" component needs to be prepared, which describes the basis for advocacy from the community level up to ministerial levels. For example, should advocacy at governmental level focus on the links between anemia and economic or social development, poverty alleviation, or human-resource development? Should the knowledge of the early childhood cognitive deficit caused by childhood anemia form the crux of an advocacy strategy, or the links between anemia and maternal mortality? Ultimately, strategies should be tailored to who is to be influenced, so that a variety of approaches is likely to be required. Public mobilization too will be crucial to raise awareness of the problem and possible solutions and to generate a demand for appropriate policy and programmatic action.

Reassessment

Programming is a cycle, not a discrete event, and the iron-deficiency problem will need to be regularly reassessed and the program monitored so as to make necessary modifications and improve effectiveness.

Programs should have clearly defined, built-in management-information systems including specifications for routine monitoring of key process and outcome indicators. Supplies, logistics, coverage, compliance, and other process and outcome indicators need to be included. Quality control through periodic sampling should be carried out, for example, with supplements or fortification levels of a foodstuff. The system should be designed so that the information it generates is made available to people who will use it to improve the functioning of the program.

Regular surveillance may be achieved through routine clinic-based data on the iron status of vulnerable groups, complemented by periodic community-based assessments. Clinic-based data is obviously to some extent biased toward those who actually attend the clinics and may miss a significant proportion of those who are most at risk. For this reason, clinic data cannot be used to estimate population prevalences. However, such data may be adequate for monitoring the outcome trend, unless there is some sudden change in normal health-service coverage over time.

Periodic evaluations of effects are also essential, despite being relatively neglected to date. Without a knowledge of progress toward the outcome objectives and thus ultimate goals, programs that are ineffective or only partially effective may be perpetuated, thus inefficiently using or even squandering limited resources. Baseline outcome data, collected before program initiation, are essential requirements for evaluations.

CONCLUSIONS

Iron deficiency is highly prevalent in the developing world as a result of various causes at different levels. Underlying most of these is poverty. Lack of purchasing power to afford foods containing heme iron or to afford the time or transport costs to access antenatal services, poor access to health services, inadequate water supply, poor sanitation, and so on all coexist in poor households living in marginalized environments where anemia rates invariably are highest. The poor social status of women is another relevant basic cause. At more immediate levels, low iron intake, poor bioavailability of dietary iron, and infection and parasitic infestation combine to jeopardize an individual's iron status, particularly at certain stages of the life cycle.

Anemia is so pervasive in the developing world, and its intergenerational effects so devastating — including debilitating fatigue, compromised immune function, widespread maternal death in childbirth, damage to the fetal brain, premature delivery, intrauterine growth retardation, raised perinatal mortality, and the failure of the child to grow well and develop physically and mentally — that there need be no further justification for concerted action now.

Standing out from the array of issues and questions, two main interrelated factors crop up repeatedly — advocacy and communication. There remains a lack of awareness of what anemia is and does, and of effective communication, from the community up to ministerial levels. Even if iron-deficiency anemia is perceived as a significant health problem, it is usually not viewed as a priority. The full range of its debilitating short- and long-term consequences — physical, mental, economic, and social — remains unrecognized by many.

Such a lack of priority is reflected in low sectoral budget allocations, the reluctance to initiate, at minimum, feasibility studies for fortification, and poor or nonexistent monitoring and evaluation systems. At district and peripheral levels, in supplementation programs at least, this is manifested as erratic and inadequate supply and distribution of tablets, poor training and supervision of front-line workers, and inadequate counselling and follow-up of intended beneficiaries. Even if sufficient supplies have reached a distribution centre, supplementation often loses out in the range of competing duties of overworked health workers.

Of course problems of access are not specific to iron-deficiency control, affecting as they do the entire system of primary health care, but even within these confines there is much scope for improvement. The fact that iron supplements have been known for so long to be efficacious in preventing and controlling anemia and yet so little success has been achieved in large-scale programs should now be consigned to history. The constraints to effectiveness are known and the technologies and systems exist, the requirement now is for priority concerted action.

The web of multiple, interacting causes of anemia demands strategies of prevention and control that act complementarily at different levels and across different time horizons. There is no one single intervention to be universally advocated — deciding what, out of an array of possibilities, to do is not an "either/or" situation, but a "both–and" one. Supplementation of at-risk groups, fortification, dietary modification, parasitic-disease control, and overall education of policy-makers, professionals, and the public all have their place. Their relative prerequisites, costs, constraints, and opportunities all need to be explored in any given situation to determine the appropriate intervention mix.

There are no magic bullets. If, for example, the new small-dose, low-cost, low-frequency preparations with fewer side-effects are found to be biologically effective, they may help remove some of the problems currently besetting supplementation programs; however, they are not a panacea. In the wider picture, technological problems are not nearly as serious as operational ones related to making programs work in communities where iron-deficient people live. The human aspects of advocacy, communications, social mobilization, participation, and behavioral change will remain integral to progress.

Other priority needs include minimal monitoring and evaluation, pertinent local-level education of both beneficiaries and community-based workers, and greater community participation. Many of

these needs interact and are mutually reinforcing. For example, better education on the benefits of reducing anemia should promote a greater community participation in programs and a greater demand on governments to deal with the problem through allocating sufficient resources to building and sustaining effective interventions. Adequate process and outcome monitoring and documentation is paramount within any approach, so that both obstacles and opportunities can be made apparent and others can learn from the experience. A budget line for operational research should also be built into large-scale programs.

Finally, in addition to public demand and community ownership, the sustainability of programs will require maximal integration of approaches into existing systems as well as transdisciplinary coalitions between different sectors in both public and private spheres, and an attack on the causes of problem at all levels — immediate, underlying, and basic.

ANNEX I

SUMMARY OF MAIN ISSUES

Some of the main issues, constraints, and questions identified in this overview are summarized here for easy reference. This is not a comprehensive list, and the detail is found in the preceding text, but it does include most of the main issues to be addressed in moving action forward.

Overall

A pressing need remains to improve the definition of the problem to be addressed. To what extent should a priority focus be on iron deficiency in addition to iron-deficiency anemia? This relates to the need for research to continue to investigate the functional impairments associated with nonanemic iron deficiency.

For all large-scale programs, data on operational effectiveness are required. Management information systems and effective, simple means of monitoring and evaluation, using key process and outcome indicators, need to be built into any new program.

Better documentation and dissemination of programmatic experiences is required to facilitate learning from success or failure.

Work is needed on devising appropriate advocacy and communications strategies, methods, messages, and media from the community to governmental levels. Training requires a greater emphasis on improving interpersonal communications skills and social mobilization at all levels.

Better communication, leading to better coordination, between public and private sectors and forums for such communication should be established, particularly for fortification.

There remains a dearth of anemia-prevalence data in many countries and population subgroups within countries. Options for practical surveillance systems, for example, sentinel sites, need further exploration.

There is a need to know more about the etiologies of anemia in various situations so as to design appropriate programmatic responses — particularly where etiologies are more complex, such as in some parts of sub-Saharan Africa.[18]

Methods for assessing iron status still need further development. A simple, noninvasive, rapid, and reliable field-based method of detecting iron-deficiency anemia at the community level remains to be found.

Iron deficiency is difficult to detect in populations where there is a high level of infection, and hence raised serum ferritin, and in infants and children with recurrent infection.

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[18] See the forthcoming report of the Expert Consultation on the Determinants of Anemia, organized and hosted by the Micronutrient Initiative in Ottawa, Canada, 16–17 September 1997.

Supplementation

The appropriate dose, frequency, duration, type, and packaging of supplement for young children requires further work.

Other aspects of supplementation that require study are:
- Is a liquid formulation feasible?
- Can other micronutrients be included, for example, zinc? What would this do to bioavailability?
- What is the potential benefit of multinutrient formulations for pregnant women? What are the options?
- What channels are most appropriate for preventive supplementation of adolescents?
- What is the feasibility of social marketing?
- What options exist for community-based distribution?
- What is the most appropriate type of strategy to ensure compliance?

Dietary Modification

There is a need overall to better understand what is actually achievable by dietary modification approaches for women and children.

What are the net bioavailabilities of different diets — specifically:
- The biological effectiveness of consumption of certain vegetables and fruits for improving iron status,
- The effects of fermentation, malting, and cooking on bioavailability, and
- Nutrient interactions and their cumulative effect on bioavailability.

A database on iron bioavailability of common diets might be useful.

What advocacy approach is required to make iron deficiency more "visible" and its effects better understood? Operational research is needed on social-marketing approaches to behavioral change. Communications approaches need to consider how to deal with the fact that heme iron is expensive, and how to address intrahousehold maldistribution of food.

Fortification

There is an urgent need for many countries to initiate studies of the feasibility of fortification that systematically investigate the presence of the various prerequisites described in the section *Fortification* (page 44) in the main paper.

In some countries, food regulations that govern the foods to be fortified, the type and levels of fortificant, labeling, quality assurance, safety, monitoring, and so on need strengthening.

Research on the long-term effect of iron–EDTA on the absorption of other nutrients is required.

Options for simple community-based enrichment, for example, adding premixes, at community levels needs further investigation, as do options for multiple-nutrient fortification where several deficiencies are found to coexist.

- How can alliances be built between public and private sectors?
- How can EDTA of an acceptable standard be made affordable?

Parasitic Disease Control
Helminths
- What is the efficacy of anthelminthic treatment of pregnant women?
- What is the cost-effectiveness of helminth control when added-on or complementary to other approaches?

Malaria
- What is the contribution of malaria and iron deficiency to infant anemia in malaria-endemic regions?
- What antimalarial prophylaxis is most appropriate for pregnancy?
- Is it safe and effective to provide iron supplements to infants and young children in malaria-endemic areas?

ANNEX II

THE PRACTICAL SIGNIFICANCE OF IRON OVERLOAD FOR IRON-DEFICIENCY CONTROL PROGRAMS

Introduction

Iron Deficiency and Anemia

Iron deficiency is the most common nutritional disorder in the developing world (ACC/SCN 1991) and the most common cause of nutritional anemia in young children and women of reproductive age. It is estimated that 2,150 million people are iron-deficient of whom 1,200 million are anemic (WHO 1991). Regional data show very high prevalences of anemia for adult women in South Asia (60%), South-East Asia (50%), and most regions of Africa (40–50%). For the subset of pregnant women, figures are as high as 75% in South Asia, 63% in South-East Asia, and over 50% for most of Africa (WHO 1992). The consequences of anemia include debilitating fatigue, compromised immune function, increased risk of maternal death in childbirth, damage to the fetal brain, premature delivery, intrauterine growth retardation, raised infant mortality, and the failure of the child to adequately grow and develop, both physically and mentally.

Public-health interventions such as the fortification of a staple food with iron, or the use of iron supplements, are being increasingly seen by planners and policy-makers as cost-effective ways of improving the iron status of populations in developing countries. Concern has been expressed, however, that such interventions might be harmful to the health of certain individuals who might be at risk from chronic disease because of high iron intakes. Attention has focused primarily on food-fortification approaches, which are usually untargeted.

This statement[19] reviews the current state of scientific knowledge of iron overload. It concludes that the risk to public health in developing countries from the increase in iron intake that is possible from a food-fortification program would be virtually nonexistent and vastly outweighed by the potential benefits.

Physiological Control of Dietary-Iron Absorption

Normally, protection against excess iron is provided by the body's regulatory mechanism whereby, if intake is held constant, the amount of iron absorbed from the diet is inversely related to the body's iron stores.

Note: References cited in this paper have been incorporated into the main reference list.

A recent detailed study of such regulation of iron absorption concluded that there is a very effective control of dietary-iron absorption in healthy subjects (Hallberg and Hulten 1996a). In both men and women of various iron statuses, consuming diets with different bioavailabilities, a threshold was found representing the maximal stores derivable from dietary iron. Iron will not accumulate in the body above these thresholds — 60 and 50 μg/L serum ferritin, corresponding to iron stores of 600 mg and 500 mg for men and women, respectively. Both nonheme- and heme-iron absorption were effectively down-regulated.

In an earlier study among women, iron absorption was found to be concordant with iron requirements and the authors concluded then that "the powerful control of iron absorption implies that dietary iron overload cannot develop in normal subjects, even with diets having high iron content or high bioavailability" (Hulten et al. 1995). Other corroborative evidence comes from epidemiological studies and studies of the effects of fortification. In epidemiological studies, it has been observed that median serum ferritin values are maximal in the third to fourth decade in men (Pilch and Senti 1984; Leggett et al. 1990b). The fortification studies are discussed in *Iron Overload and Iron Fortification* (page 79).

Iron Overload

Iron overload refers to an excess of iron in the body that, under certain conditions, may have harmful effects (BNF 1995). It occurs when excess accumulated iron eventually overwhelms the cellular mechanism for safe storage (Walters et al. 1975; Gordeuk 1992) resulting in multisystem iron toxicity, which may in turn become manifest in later life as various chronic diseases such as cirrhosis of the liver, diabetes, hypermelanotic skin pigmentation, arthritis, and heart failure (Peters and Seymour 1976; Weintraub et al. 1988).

Iron overload has been defined with respect to two indicators, transferrin saturation and serum ferritin. A transferrin saturation of >60% in men or >50% in women or a serum ferritin level of >300 μg/L in men and >200 μg/L in women, or both, have been suggested as cut-off points defining iron overload by the British Nutrition Foundation (BNF 1995). There are three main types of iron-overload disease: excessive iron absorption from a normal diet, sub-Saharan iron overload, and iron accumulation from blood transfusion.

Excessive Iron Absorption from a Normal Diet

Excessive iron absorption from a normal diet is often referred to as primary overload. Most overload disease in populations who trace their recent origin to the European continent falls into this category and is related to hereditary hemochromatosis, a genetic disorder that is present in a small percentage of such population groups who are homozygous for the iron-loading gene. Homozygosity for this defective gene results in deficient activity of a protein that directly or indirectly affects iron metabolism (Gordeuk 1992).

In addition to hereditary hemochromatosis, such excessive iron absorption is also seen in certain genetic and acquired blood diseases in which there is markedly increased but ineffective red blood cell production (erythropoiesis) that stimulates iron absorption by some unknown mechanism (Pootrakul et al. 1988). Examples of such iron-loading anemias include thalassemia major and the rarer sideroblastic anemias.

Hereditary hemochromatosis[20]

Individuals with hereditary hemochromatosis absorb about 2 mg iron daily (Walters et al. 1975) leading eventually to clinical manifestations of iron overload, usually between the fourth and sixth decades of life. About 0.1–0.5% of populations of European extraction have hereditary hemochromatosis — a range that covers the prevalences found in studies in Australia (Bassett et al. 1982), Canada (Borwein et al. 1983), France (Beaumont et al. 1979), Sweden (Olsson et al. 1983; Hallberg et al. 1989), and the USA (Expert Scientific Working Group 1985; Cartwright et al. 1979; Dadone et al. 1982; Edwards et al. 1988). Most patients have been found to be of Celtic origin, that is, from Scotland or Ireland (Jazwinska et al. 1995). In a very careful and extensive study in Finland, a lower prevalence of 0.05% was found (Karlsson et al. 1988).

A recent study examined the postulated Celtic origin of the hemochromatosis gene and investigated gene frequencies in individuals originating from Algeria, Ethiopia, and Senegal (Roth et al. 1997). No cases of the particular disease-causing genetic mutation were found.

The considerable variation in estimated prevalences may reflect true differences or different definitions of hereditary hemochromatosis, or both. Some definitions refer to homozygosity for the defective gene whether actual iron-overloading has occurred or not (Edwards et al. 1988), whereas others refer to the presence of established iron overload (Hallberg et al. 1989).

It should also be emphasized that hereditary hemochromatosis is an autosomal recessively inherited disorder, which means that the prevalence is not evenly distributed in populations with the gene, but rather occurs in "genetic hot spots" where people are living in different forms of isolates favouring intermarriage (Hallberg, personal communication[21]). Such isolates may be geographical, linguistic, religious, or economic, for example. This is also likely to be a factor behind the large variations in prevalences reported in different parts of the world.

Although hereditary hemochromatosis has been reported as mainly affecting individuals with European extraction (Powell et al. 1994), recent evidence has emerged that primary overload may also occur among individuals with African extraction (Barton et al. 1995; Wurapa et al. 1996; Yip et al. 1996a), although there is no information yet on its prevalence. This is also thought to be genetically mediated — albeit in a different way to hereditary hemochromatosis.

Among homozygotes for hereditary hemochromatosis, there is a long asymptomatic period during which the condition may go undiagnosed. It has been estimated that 20% homozygotes will progress to overt tissue damage and symptomatic disease (Finch and Huebers 1982), and that overload is 2.7 times more common among men than women (Edwards et al. 1980). The development of such clinical complications is related to extraneous factors that either potentiate the liver damage caused by excess iron (such as alcohol consumption, drug use, and viral infections), reduce the rate at which iron accumulates (such as menstruation and blood donation), or reduce the oxidative damage it causes in excess (for example, antioxidant intake) (Crosby 1987; Olsson 1994).

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[20] Extensive, regularly updated research findings and information on hereditary hemochromatosis may be found at the following web site: http://www3.ncbi.nim.nih.gov:80/htbin-post/Omim/dispmim?235200

[21] Hallberg, L., 26 November 1997; Terrassgaten 11, S-41133 Goteborg, Sweden.

In addition to those homozygous individuals with hereditary hemochromatosis, around 7–15% of such populations are heterozygous for the gene (Edwards et al. 1988; Leggett et al. 1990a; McClaren et al. 1995). Although such individuals may exhibit modest increases in body iron, they do not clinically manifest overload (Bothwell et al. 1978; Bothwell 1983; Cartwright et al. 1979; Powell et al. 1994; Bulaj et al. 1996).

In an Australian study in which 98 heterozygotes were compared to normal individuals, there were no significant differences in serum ferritin, and repeated liver biopsies in 11 subjects revealed no development of iron overload over a 4- to 16-year follow-up period (Bassett et al. 1982). Two other studies found that transferrin saturation was partially elevated in heterozygotes, but that serum ferritin was not (Cartwright et al. 1979; Crawford et al. 1995). One study concluded that iron stores in these heterozygous individuals would increase as a result of dietary-iron fortification but that regulation of iron absorption would be sufficiently effective to prevent clinically significant iron accumulation (Bezwoda et al. 1981).

The prevalence of iron deficiency has been found to be lower in a female heterozygote population as compared to a female control population (Crawford et al. 1995), and it is quite possible that heterozygosity protects against iron deficiency. The gene for hemochromatosis may be perpetuated by the selective reproductive advantage it confers to women who live in populations where iron-deficiency anemia is common — given the links between iron-deficiency anemia and maternal mortality risk.

It is likely that most individuals who suffer from hereditary hemochromatosis tend to reside in countries where screening and prophylactic measures are likely to be feasible and effective. In a recent draft, the US Centers for Disease Control and Prevention (CDC) recommends, for the US population, secondary prevention by screening and case-finding of hereditary hemochromatosis in the asymptomatic latent period (Edwards and Kushner 1993; Haddow and Ledue 1994; Yip et al. 1996a) using transferrin saturation as a screening indicator (Skikne and Cook 1987). With proper management, individuals detected as having hereditary hemochromatosis in the subclinical phase can have the same outcome and life expectancy as normal individuals (Edwards and Kushner 1993). For those cases detected, the clinical manifestation of disease is prevented or treated by removal of body iron by repeated phlebotomy (blood letting) or blood donation.

In developing countries, where screening is unlikely to be feasible, the prevalence of hereditary hemochromatosis is largely unknown. Definitive figures on relative prevalence rates should soon be available because the gene has now been isolated and tests for its identification have been developed. The gene is known to be linked to the HLA locus on the short arm of chromosome 6 (Gordeuk 1992).

Iron-loading anemias

In iron-loading anemias, ineffective erythropoiesis increases gastrointestinal iron absorption, which can contribute significantly to the iron burden and lead to iron overload. The prevalence of homozygous forms of thalassemia may be as high as 1%, particularly in northern Africa, the Middle East, and Asia (WHO 1983). Such individuals accumulate up to 4–5 mg iron daily (which is considerably more than individuals with hereditary hemochromatosis) and will clinically

manifest overload by their second decade of life. Much larger proportions of the population are heterozygous carriers of such common hemoglobinopathies as sickle-cell trait, beta-thalassemia minor, and asymptomatic alpha-thalassemias, but again there is no tendency to iron overload among these individuals (Mohler and Wheby 1986; Fleming 1996).

Although sickle-cell anemia is associated with abnormally high iron absorption (Erlandson et al. 1962), iron overload is not a clinical problem (Isah et al. 1985; Serjeant 1985), probably because patients are not subjected to high blood-transfusion regimens as are standard for thalassemia major. Many patients with sickle cell will die young.

Sub-Saharan Iron Overload

A second type of iron overload has been found among African traditional beer-drinkers (Bothwell and Isaacson 1962) and is related to excess iron absorption from drinking beer brewed in iron pots. The beer provides an acidic medium that helps leach iron from the pots, as well as itself containing iron-complexing ligands that further enhance bioavailability. About 100 mg iron per person per day is consumed in this way and large proportions, predominantly male, may develop iron overload. (For comparison, about 14 mg of less bioavailable iron is consumed per person per day in a typical western diet (Bothwell et al. 1979; Stevens et al. 1988).)

Such an overload condition has inaccurately been referred to in the past as "dietary overload." This is inaccurate because, first, the iron intake is unphysiologically high and comparable with therapeutic iron doses and, second, some evidence is now also suggestive of a genetic component here too. The regulation of the absorption of a therapeutic dose of iron is not controlled in the same way as dietary-iron absorption by iron stores, but rather by the iron requirements of the bone marrow. This may, in certain unusual cases such as this, lead to the accumulation of excess iron.

Sub-Saharan iron overload has been found to exist in 15 countries in sub-Saharan Africa, predominantly southern Africa, although it is reported to be less prevalent now because, first, professionally brewed beer is now available to the general population and, second, the drums used for traditional brewing are as likely to be steel as iron (Gordeuk 1992). Nevertheless, the condition still persists in up to one-fifth of male traditional beer-drinkers in rural areas (Gordeuk et al. 1986; Gordeuk 1992; Fleming 1996). In contrast, Ethiopian adults who consume 300–500 mg iron daily do not suffer from overload, as most of the iron is unavailable contamination-iron derived from iron-rich soil. Despite being over 10 times as prevalent in many parts of Africa as homozygosity for hereditary hemochromatosis is among people of European extraction, sub-Saharan iron overload has received less attention from the medical community in recent years (Gordeuk 1992).

There is also some suggestive, but not conclusive, evidence of a genetic predisposition to this condition, which is different to that in hereditary hemochromatosis (Gordeuk et al. 1990; Wurapa et al. 1996). Not all individuals who consume excessive amounts of beer manifest iron overload. The presence of an iron-loading gene may result in homozygotes developing iron overload and the possibility of a genotype-by-environment interaction that results in heterozygotes who also drink traditional beer developing iron overload too (Gordeuk 1992). If such a genetic causal factor is

confirmed, this will provide further indirect evidence that the absorption-regulatory systems of normal individuals have the capacity to protect the body from very large quantities in the diet (Bothwell 1996).

Iron Accumulation from Blood Transfusion

A third type of iron overload — often called secondary overload — is related to excess iron accumulation from frequent blood transfusions that are needed to treat iron-loading anemias such as thalassemia major and intermedia (Pippard 1994) that have been described earlier.

Individuals with thalassemia major, if transfused regularly up to the normal prescribed hemoglobin level of 100 g/L, no longer have abnormal iron absorption. If they remain with a low hemoglobin, however, excessive iron accumulation continues, leading to liver cirrhosis due to hemosiderosis (Heinrich et al. 1973). Other transfusion-dependent conditions include anemia as a result of bone-marrow failure and various types of severe chronic hemolytic anemia. The main prescribed therapy in developed countries is long-term use of an iron-chelating agent to reduce body iron load.

Iron Overload and Iron Fortification

The effectiveness of the downregulation and eventual blocking of iron absorption when iron stores of the recipient are high has been described (see *Physiological Control of Dietary-Iron Absorption*, page 74). This also applies to fortification iron. Most kinds of iron used for fortification are only partly soluble and thus only partly potentially bioavailable. The fraction that does dissolve will enter the nonheme iron pool and its absorption will be governed by the same mechanism as nonheme iron from other sources. Fortification studies have shown that serum ferritin was not elevated in iron-replete men (Ballot et al. 1989) even after addition of high doses of vitamin C for 2 years (Cook et al. 1984). In one study of an iron-replete man, a daily dose of 10 mg iron as ferrous sulphate over 500 days failed to produce a significant increase in serum ferritin (Sayers et al. 1994). Two extensive necropsy studies — one in subjects from 18 countries — show no further increase in liver iron stores after about 30 years of age (Charlton et al. 1970; Sturgeon and Shoden 1971). Further corroborative evidence comes from a recent study of 31 men (Hallberg et al. 1997) in which the relevance for iron fortification was directly addressed. The authors conclude that, for normal subjects, there is no risk of iron overload arising from an iron-fortified diet.

A concern was expressed in the 1970s that the extra iron from fortification would precipitate clinical hemochromatosis earlier than if it there was no fortification or that heterozygous carriers might become iron-accumulators (Crosby 1975, 1978; Finch and Monsen 1972). The experiences of iron fortification in Sweden and the USA are relevant here.

In the USA, only 25% of dietary iron intake could be removed if fortification was stopped (Raper et al. 1984) and the bioavailability of fortificant iron is largely unknown. The 75% that remained would still predispose susceptible individuals to eventual clinical manifestation of disease — particularly because of the high proportion of dietary iron in the heme form. The combined effects of food fortification with iron, which was initiated in 1940, and iron supplementation in the USA have not been found to accelerate the manifestation of clinical hemochromatosis and there is no

evidence of any increase in the incidence of hemochromatosis from mortality, morbidity, or health-survey data (Gable 1992; Bothwell 1996).

The CDC has concluded that stopping fortification in the USA would not make any difference to the susceptibility of an individual with hereditary hemochromatosis to iron overload (Yip et al. 1996a). Unless detected and treated, susceptible individuals would eventually develop iron overload regardless of whether iron fortification programs were underway in the population or not.

In Sweden, iron fortification started in the late 1940s, with iron-fortificant levels that were higher than anywhere else, providing 42% of dietary iron intake (Westin 1975). Studies have since shown, however, that only about 15% of this carbonyl iron — the best iron fortificant commercially available — actually joins the nonheme iron pool and becomes potentially available (Hallberg et al. 1986), which would correspondingly reduce the contribution of fortified iron to the overall diet. Despite one study (Olsson et al. 1978) that reported a high incidence of hemochromatosis among men presenting at a single small district hospital (which the authors did not in fact associate with fortification), no noticeable increase has been found at a national level in the incidence of iron overload (Lindmark and Eriksson 1985; Hallberg et al. 1989). These latter authors found a prevalence of hereditary hemachromatosis of 0.1% in these extensive population studies. Recent studies have shown that the per-caput daily absorbed iron intake in Sweden has decreased by 12% since iron fortification ceased and phlebotomies among men with hereditary hemochromatosis are required somewhat less frequently now (Olsson, personal communication[22]).

In a recent paper, the issue of potential iron overload among the South African population is addressed in considering the need for a national iron-fortification program (MacPhail et al. 1997). The authors carefully consider all aspects of overload risk and conclude by recommending strongly that a food-fortification strategy be developed, for many of the same reasons offered here — this despite the existence in South Africa of iron overload related to beer consumption.

Iron Status and Coronary Heart Disease

Iron status has been linked to the risk of both coronary heart disease and cancer. The theory is that iron, as an oxidant, can cause cellular changes leading to arteriosclerosis or tumour formation (Beard 1993).

About 35 years ago, evidence first emerged of an association between low hematocrit values and lower risk of coronary heart disease (CHD), but the suggestion then was that the low blood viscosity in premenopausal women could explain their low risk of CHD compared with men (Stokes 1962). Low iron stores, as measured by serum ferritin, were first suggested as contributing to the lower risk of CHD among women nearly 20 years later (Sullivan 1981). International comparisons of liver iron stores and CHD mortality provided further epidemiological evidence (Lauffer 1991), albeit very weak as these were largely bivariate correlations without

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[22] Olsson, S., 12 January 1997; Department of Medicine, Oestersund Hospital, S-831 01 Oestersund, Sweden.

controlling for confounding factors. There has been no confirmation of such an association from case-control studies in Scotland (Riemersma et al. 1991) and the USA (Stampfer et al. 1993).

The most convincing evidence of an association between high serum ferritin and CHD came from a prospective 3-year follow-up study of 2,000 middle-aged Finnish men (Salonen et al. 1992), which showed men with high serum ferritin to be at least twice as likely to contract CHD as others, after controlling for confounding. A prospective Canadian study found CHD risks to be similarly elevated, but only for men and women with abnormally high serum-iron concentrations suggestive of overload (Morrison et al. 1994).

In contrast, several prospective studies failed to show an association, including a reanalysis of the 1971–1987 data set from the US National Health and Nutrition Examination Survey (NHANES) (Cooper and Liao 1993), a further follow-up of NHANES people (Sempos et al. 1994), and a study in Iceland (Magnussen et al. 1994). No significant increase in the risk of myocardial infarction with respect to total dietary iron or nonheme iron intake was found in a study of nearly 45,000 American health professionals in 1986 (Ascherio et al. 1994). Heme iron, however, was associated with the risk of myocardial infarction and of fatal CHD but only among men who were not taking vitamin E supplements or were diabetic, or both. It is possible that dietary heme in excess may increase coronary risk only in the presence of oxidative stress from other sources.

It is also pertinent that neither morbidity or mortality from CHD is increased among subjects with hereditary hemochromatosis (Powell et al. 1993). Finally, a study of trace metal content of cardiac muscle confirmed the lack of any relationship between iron content of either serum or tissue and the presence of CHD (Oster et al. 1989) and it has been claimed recently that it is unlikely that any association between serum ferritin and CHD is a true reflection of iron-induced disease (Burt et al. 1993).

It is important to realize that the biochemical indicators for iron status used to indicate high iron stores — transferrin saturation and serum ferritin — may themselves be influenced by chronic disease processes (Lipchitz et al. 1974; Yip and Dallman 1988; Alexander 1994) and it is quite possible that this is giving rise to the apparent association (Weiss et al. 1993; Yip 1994). In a separate analysis, the link between iron stores and serum ferritin has also recently been shown to be rather weak Only half the variation in iron stores can be ascribed to a variation in serum ferritin and vice versa (Hallberg and Hulten 1996b; Hallberg et al. 1997).

Iron Status and Cancer

It has been suggested that high serum ferritin predisposes to cancer (Stevens et al. 1988; Weinberg 1992), although this remains controversial. It is necessary to distinguish the risks attached to severe iron overload from those associated with iron parameters at the high end of the normal range.

Regarding severe iron overload, there are plausible scientific explanations for the increased incidence of liver cancer and indeed this is a significant cause of death in individuals with hereditary hemochromatosis, particularly when cirrhosis is present (Niederau et al. 1985; Fargion et al. 1992). Thalassemia sufferers also have an increased risk of general cancer (Zurlo et al.

1989) and miners of iron ore have been found to have greater risk of lung and laryngeal cancer (Cole and Goldman 1975).

Such associations, however, do not reflect the relationship between cancer risk and iron status in the normal range of the population. Prospective studies in Finland, Taiwan, and the USA have provided direct evidence to suggest that high body-iron stores increase cancer risk (Beasley et al. 1981; Stevens et al. 1988; Stevens 1993). In addition, international and subnational epidemiological studies in Europe and Italy, respectively, suggest a positive association between meat consumption (and thus heme iron) and cancer mortality (Decarli and La Vecchia 1986; Merlo et al. 1991) — although this is weak indirect evidence of a causal link given the lack of control for confounding.

Direct evidence, from cohort or case-control studies, linking high iron status with cancer risk is very limited. The British Nutrition Foundation (BNF) Iron Task Force recently reviewed 35 cohort or case-control studies relating types of food to the risk of breast or colorectal cancer (BNF 1995). A positive association does appear between meat consumption and both breast cancer and colorectal cancer, although the evidence directly implicating iron is judged to be inconsistent and rests on the assumption that iron stores are directly related to meat consumption. The BNF report concludes that "it is difficult to see how modest increases in iron status could favour development of tumours" (BNF 1995).

Excess Iron and Infections

In an infected individual, iron is needed both by the individual as well as the infectious agent. The links between excess iron and malaria have been studied most frequently in this regard. Iron deficiency does not protect against malaria (Snow et al. 1991), but parenteral iron is reported to increase the risk of respiratory infections and the prevalence and effects of malaria in infants (Oppenheimer et al. 1986a, b; Smith et al. 1989). Standard oral iron supplements given to infants in the Gambia have been found to be followed by more frequent fever associated with severe malaria parasitemia (Smith et al. 1989), although these observations were not confirmed in infants in Cameroon (Chippaux et al. 1991), older children in the Gambia (Bates et al. 1987) or Papua New Guinea (Harvey et al. 1989), nor in pregnant women in the Gambia (Menendez et al. 1994). After treatment of malaria in Gambian children, iron supplementation was not associated with increased prevalence of malaria, but with a better hematological response (Boele van Hensbroek et al. 1995).

The evidence supporting a direct effect of iron on malaria growth is weak (Peto and Thompson 1986) and the prooxidant theory of iron toxicity has been judged to fit better (BNF 1995). The inflammatory response after malaria infection, plus the hemolysis, releases tissue iron that may exacerbate free-radical damage in the tissues. The higher the iron status, the greater is the potential damage or disease severity (BNF 1995).

Sickle-cell trait and sickle-cell anemia are other considerations with respect to malarial infection and iron control. Sickle-cell anemia is not very prevalent because of the high mortality of affected individuals during infancy. Among pregnant women with sickle-cell trait (18% of that population), iron supplementation has been found in a randomized, double-blind, placebo-controlled trial in the

Gambia to be associated with a reduced hematological response, increased frequency of placental malarial infection, and reduced birth weights on delivery (Menendez et al. 1995). Women without sickle-cell trait on the other hand benefited, with respect to iron status and birth weights, from supplementation. Finally, a randomized, double blind, placebo-controlled trial of iron or anti-malarials, or both, in prophylactic oral dosages in normal and sickle-cell-trait infants has recently been completed and is currently being analyzed.

The chief researcher in many of these recent studies has concluded that iron-deficiency control programs (either food fortification or pharmaceutical supplementation) must continue to be promoted in developing countries, but that their effect on malaria should be monitored, especially in special groups of individuals such as those with sickle-cell trait (and perhaps other overload conditions) who may constitute a considerable proportion of the population (Menendez, personal communication[23]).

Conclusions

The evidence relating to the risk that some individuals in populations consuming iron-fortified foods will develop iron overload, or develop it earlier, has been reviewed. Studies linking iron status to hereditary hemochromatosis, iron-loading anemias, sub-Saharan iron overload, and transfusion-dependent overload conditions have all been described, as have the relationships between iron status, risk of cancer and CHD, and infection.

Iron-deficiency anemia is extremely widespread in many developing-country populations. The data are clear. The efficacy programs to prevent and control iron deficiency, such as iron supplementation and iron fortification, in improving iron status is also well known. The question of whether to act to prevent or control iron deficiency, or not to act in the hope that some individuals will not develop iron overload or develop it later, is a risk–benefit question. Figures are not available to fully quantify such risks and benefits at present — largely because prevalence data on conditions predisposing to iron overload, and the effect of interventions on the manifestation of overload, do not exist for developing countries. However, the following is known:

- First, iron fortification will not lead to the development of iron overload among normal individuals. This is because there is a very efficient system of down-regulation of dietary-iron absorption and an actual blocking at certain iron-store thresholds. This applies to diets with high iron bioavailabilities, high heme-iron content, and to iron-fortified diets.
- Second, several genetic conditions predispose to risk of iron overload. The risk has been found to be related to homozygosity of a defective gene. Individuals who are homozygous have been found to be a small minority, among populations of European extraction, and largely concentrated in "genetic hot spots" not evenly distributed throughout the population. Heterozygotes, who are more numerous, are not at risk of iron overload. There are few data on the prevalence of hemoglobinopathies in developing-country populations.
- Third, the amount of iron added to the diet through fortification could make a significant rightward shift in the iron-status distribution of an iron-deficient population. Fewer people

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[23]Menendez, C., 12 December 1996; Corporacio Sanitaria Clinic, Villaroel 170, Barcelona 08036, Spain.

would become anemic. However, such amounts would make little or no difference to the outcome for those with various hemoglobinopathies, or indeed to those individuals who develop sub-Saharan iron overload. The latter is a unique case and related to a dose that could be considered therapeutic and far above what might be provided by fortification. In addition, it is thought likely that this form of overload is also genetically mediated.

A recent review in the USA has concluded that food-fortification iron does not significantly increase the prevalence of overload or the rate at which it develops, and that withdrawal of iron-fortified foods plays no role in its management. This is a population where the iron status is considerably higher than most developing countries.

A rare clinical problem in a small minority of individuals should not, in any case, be addressed with a public-health approach — in this case withholding iron supplementation or fortification programs from the population at large. The proper approach in developed countries to management is a clinical one, based on case-finding through screening using biochemical tests. In developing countries, where such an approach may not be feasible, process and outcome monitoring will remain of paramount importance. There has always been a need to monitor iron concentrations in fortified foods, from the premix to the final product, and this should be combined with monitoring the effect on the iron status of the population. This will be particularly important in malaria-endemic populations and those with sickle-cell trait.

The evidence relating iron status and risk of CHD and cancer remains controversial. Even if an association with high iron stores were found to exist in future, this would not be a contra-indication for programs to prevent or control iron-deficiency anemia in developing-country populations where iron status is at the other end of the spectrum. **The potential benefit of an iron intervention to a predominantly iron-deficient population is likely to vastly outweigh any risk this may pose for a few individuals.**

Action is needed to prevent or control iron deficiency where it is prevalent. The counter-argument would be that a large iron-deficient proportion of a population should be maintained in its state of deficiency with the attendant debilitating consequences described earlier. This would be done to avoid a risk, as yet unquantified, that a few individuals might become clinically ill slightly earlier. Not only is this not rational public-health policy, it is probably unethical. Although the exact quantification in future of overload risks would lead to a strengthened case, enough is known to act now to prevent the known risks that apply to the iron-deficient majority of these populations.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ACC/SCN	United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition
AIDS	acquired immune deficiency syndrome
BNF	British Nutrition Foundation
CDC	United States Centers for Disease Control and Prevention
CEC	Commission of European Communities
CHD	coronary heart disease
DALY	disability-adjusted life year
EDTA	ethylenedianibetetraacetic acid
EPI	Expanded Programme on Immunization
ESPGAN	European Society for Paediatric Gasterenterology and Nutrition
FAO	Food and Agriculture Organisation of the United Nations
FDA	United States Food and Drug Administration
GOI	Government of India
GRAS	generally recognized as safe
Hb	hemoglobin
Hct	hematocrit
HIV	human immunodeficiency virus
ICMR	Indian Council of Medical Research
IDA	iron-deficiency anemia
IIPS	International Institute of Population Sciences
INACG	International Nutritional Anemia Consultative Group, Nutrition Foundation
IQ	intelligence quotient
IUNS	International Union of Nutritional Sciences
JCHP	Joint Committee on Health Policy (UNICEF/WHO)
MI	Micronutrient Initiative
MSG	monosodium glutamate
NRC	National Research Council
OMNI	Opportunities for Micronutrient Interventions
PAMM	Program Against Micronutrient Malnutrition
PCD	Partnership for Child Development
PCV	packed cell volume
RDA	recommended dietary allowances
TBA	traditional birth attendant
UNICEF	United Nations Children's Fund
UNU	United Nations University
USAID	United States Agency for International Development
NHANES	United States National Health and Nutrition Examination Survey
WHO	World Health Organization
WIC	Women, Infants, and Children project
WSC	World Summit for the Child