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10. ABSTRACT

Provides background and guidance for designing effective public health programs aimed toward prevention and therapy of the most widespread nutritional deficiency anemia, iron deficiency. These guidelines are the result of a meeting of the International Nutritional Anemia Consultative Group (INACG) attended by representatives of most agencies concerned with iron nutrition. Nutritional anemia is widely prevalent in many parts of the world, particularly in LDCs. Folate deficiency is a factor in certain segments of the population, such as pregnant women and increasing evidence suggests that iron dificiency per se, even in the absence of obvious anemia, may affect health. The precise amount of iron needed depends on the amounts lost from the body and amounts needed for growth and pregnancy. Iron requirements of children increase during periods of rapid growth and in girls, there is a further increase in iron requirements at the onset of menstruation. Severe anemia during pregnancy is associated with an increased risk of maternal and fetal morbidity and mortality. Mild anemia is associated with an increased risk of premature delivery, low birth-weight, placental hypertrophy and reduced estriol excretion. An assessment of the iron status of a population is required to determine the need for and intervention program and to facilitate the design of the most suitable intervention strategy. Basically, two principal forms of direct intervention are available: "supplementation" and "fortification". In populations with a high prevalence of anemia, supplementation will be needed to treat the most severely affected individuals. The vehicle for fortification should be one that is already consumed in adequate amounts by the general population. Various alternatives are discussed. Pregnant women generally should be given iron supplements and other target groups, such as school children, should be considered in a population with more severe iron deficiency.

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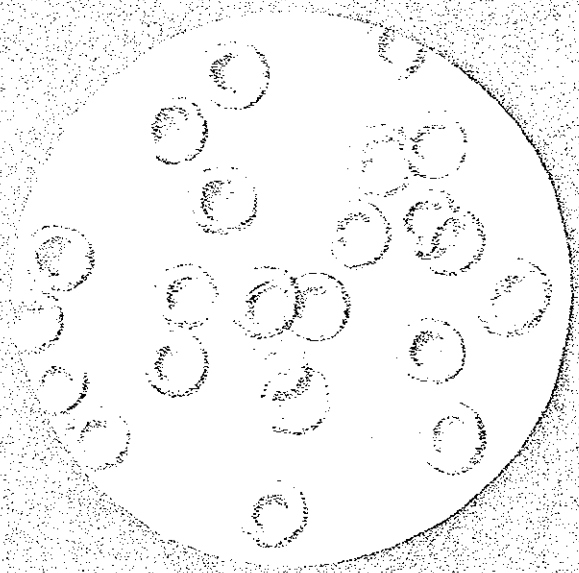

The purpose of the International Nutritional Anemia Consultative Group (INACG) is to guide international activities aimed at reducing nutritional anemia in the world. The group offers consultation and guidance to various operating and donor agencies who are seeking to reduce iron deficiency and other nutritionally preventable anemias. As part of this service, INACG has prepared guidelines and recommendations for:

—Assessing the regional distribution and magnitude of nutritional anemia;

—Developing intervention strategies and methodologies to combat iron deficiency anemia;

—Evaluating effectiveness of implemented programs on a continuing basis so this evaluation of intervention techniques is a continuing and dynamic procedure;

—Research needed to support the assessment, intervention and evaluation of programs.

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GUIDELINES FOR THE ERADICATION OF IRON DEFICIENCY ANEMIA

A REPORT OF THE
INTERNATIONAL NUTRITIONAL ANEMIA CONSULTATIVE GROUP
(INACG)

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Introduction

Nutritional anemia is widely prevalent in many parts of the world, particularly in developing countries. Although many nutrients and co-factors are involved in the maintenance of a normal hemoglobin concentration, the most common nutrient deficiency in nutritional anemia, from the public health viewpoint, is iron deficiency. Folate deficiency is a factor in certain segments of the population, such as pregnant women. Increasing evidence suggests that iron deficiency *per se*, even in the absence of obvious anemia, may affect health, so the problem may be much greater than might be indicated by data on hemoglobin concentration alone.

Effective control or elimination of anemias due to nutrition deficiencies in any particular population requires a logically formulated series of measures designed with broad understanding of the characteristics of the problem and the population affected. Assessment, intervention and evaluation are integral parts of comprehensive public health programs to improve nutriture of a population. There must be a clear description of the magnitude and severity of the problem, including the characteristics of the anemia in order to identify its etiology, and of the affected population groups. Guided by such information, logical plans for an effective intervention program can be developed. Preventive and therapeutic programs must be managed by knowledgeable personnel and integrated into the continuing health and nutrition activities within the country.

It is important that talented personnel with necessary specialized expertise be developed and utilized and that there be an active educational effort in order to inform appropriately the involved personnel concerning the differing aspects of the program. Continued monitoring is essential to assure that the measures instituted are effective and that the full benefit is enjoyed by the public.

This report provides background and guidance for designing effective public health programs aimed toward prevention and therapy of the most widespread nutritional deficiency anemia, iron deficiency.

These guidelines are the result of a meeting held in Göteborg, Sweden, in June, 1977, of the International Nutritional Anemia Consultative Group (INACG), attended by representatives of most agencies concerned with iron nutrition. INACG is supported by a grant from the Agency for International Development to The Nutrition Foundation, Inc., which acts as the Secretariat.

I.
IRON REQUIREMENTS

As with all essential nutrients, adequate amounts of iron must be absorbed to maintain optimum body concentrations. The precise amount needed depends on the amounts lost from the body and amounts needed for growth and pregnancy. Amounts lost from the body may be increased in pathological conditions.

Iron losses and hence iron requirements can be determined with a fair degree of precision. In the adult, basal iron losses via the intestine, skin and urine are about 14 μg/kg body weight/day (about 0.9 mg/day for men and 0.7 mg/day for women). In males the daily absorption of 0.9 mg/day will maintain iron balance. The female of child bearing age incurs greater losses due to menstruation. Although the amount lost each month by a given woman is fairly constant, losses vary widely among individuals. The frequency distribution of menstrual iron losses is similar in different population groups, and is skewed, 90% of women having average losses of 1.4 mg of iron per day or less. Therefore, the requirements of 90% of nonpregnant women of childbearing age can be met if a mean of 2.1 mg (0.7 + 1.4) of iron is absorbed each day. In pregnancy, a total of 500 to 600 mg of additional iron is needed. This requirement is chiefly in the latter part of pregnancy, when, to maintain iron balance, 5 mg or more may have to be absorbed each day.

Iron requirements of infants on a body weight basis are much higher than adults due to their rapid growth rate. Since the iron content of milk is low, if breast feeding is prolonged beyond the first six months of life without the addition of other iron containing foodstuffs, as is the practice in many developing areas of the world, the infants are very liable to develop iron deficiency. Such anemia commonly occurs during the last quarter of the first year.

Iron requirements of children are closely related to growth and increase during periods of rapid growth, both in preschool and schoolage children. In girls, there is a further increase in iron requirements at the onset of menstruation.

The amount of iron which must be ingested to achieve the required daily absorption depends to a large extent on the type of diet. Haem iron in animal foods is much more readily absorbed than iron in vegetables and cereals (non-haem iron). Meat products, including poultry and fish, enhance non-haem iron absorption, while some other foodstuffs inhibit it. The amount of iron absorbed from a given diet can be precisely quantitated by extrinsic isotopic labelling as described later in this report.

II.
DELETERIOUS EFFECTS OF ANEMIA AND IRON DEFICIENCY

WORK PERFORMANCE

Work capacity, under experimental conditions of near maximal work load, has been shown in a number of studies to be related to hemoglobin concentration and to be decreased in even mildly anemic subjects.[5-7] Although most jobs do not involve near maximal work loads, there is increasing evidence that milder degrees of anemia may also affect work output in everyday tasks. A study in Indonesia demonstrated a correlation between the work output of latex tappers and hemoglobin concentration.[8,9] Work output was significantly (19%) less from tappers with iron deficiency anemia than from non-anemic tappers. Another study found a significant decrease in the area of ground cleared of weeds by anemic laborers as compared with their non-anemic counterpart.[9,10] Similarly, a study in Sri Lanka[11] demonstrated a significantly smaller work output by anemic tea pickers. In some of these studies, work output increased significantly following correction of the anemia by administration of iron. These reports indicate that even moderate degrees of iron deficiency anemia may have far reaching socioeconomic consequences.

The mechanisms responsible for the alterations in work capacity and work output are beginning to be elucidated. With a marked reduction of hemoglobin and at maximal work output, limitation in oxygen carrying capacity is probably the major factor.[11] With less severe degrees of anemia and at ordinary levels of work, other factors are probably more important. Experimental evidence indicates that prolonged iron deficiency in rats impairs work capacity even in the absence of anemia. This is associated with, and possibly due to, a decrease in glycerophosphate dehydrogenase activity in the skeletal muscle. The abnormality is rapidly reversed by iron therapy.[13]

PREGNANCY

Severe anemia during pregnancy is associated with an increased risk of maternal and fetal morbidity and mortality.[14-18] Even mild anemia has been shown to be associated with an increased risk of premature delivery,[19] low birthweight,[20] placental hypertrophy,[21] and reduced estriol excretion.[19]

INFECTION

Although iron deficiency anemia is generally believed to increase an individual's susceptibility to infection there is no firm evidence to support this view. There have been few epidemiological studies relating the prevalence and the incidence of infections to iron deficiency, and the influence of confounding variables makes such studies difficult to control and interpret.[22]

Studies have shown a reduction in the incidence of respiratory infections in iron deficient anemic children supplemented with iron as compared with a comparable control group receiving only a placebo.[23,24] On the other hand, controlled trials among premature infants[25] and nonanemic children[26] failed to show any beneficial effect of iron supplementation. Basta[16] found that anemic laborers in Indonesia had significantly more infections than did nonanemic laborers and that supplementation with iron had a beneficial effect on the occurrence of infections in the anemic workers. Studies in press by Basta and collaborators (personal communication) among construction workers in Kenya describe similar findings.

Several biochemical and immunological effects of iron deficiency which may be relevant to infection are well established. In severe iron deficiency phagocytic capacity of leucocytes is decreased,[27] and myeloperoxidase activity[28,29] and lymphocyte transformation are impaired.[27,30]

Iron is a growth factor for many bacteria,[31] however, and transferrin has been shown to impair bacterial growth *in vitro*.[32] Masawe et al.[33] detected a higher prevalence of malaria infections in patients with iron deficiency anemia during treatment with iron than in control subjects. It could be argued, however, that this effect was due to an increase in the numbers of young red cells which are more easily parasitized.

In summary, although the complexity of the interaction between the infectious agent and the host makes proof extremely difficult, there is suggestive but not conclusive evidence of an increased susceptibility to infection in subjects with iron deficiency anemia.

OTHER EFFECTS

It is probable that iron deficiency may affect many bodily functions. Abnormalities such as decreased gastric juice secretion,[34] reduced activity of intestinal cell enzymes,[35] and subcellular structural abnormalities including mitochondrial enlargement[36,37] have been documented in iron deficiency. Improvement of subnormal mental performance in iron deficient infants and children has been reported following the administration of iron.[38-41] An association has been observed between growth rates and anemia in children, with an apparent beneficial effect of iron therapy.[42] This effect, however, is difficult to interpret because of the interaction of iron deficiency, reduced physical activity, anorexia resulting in a reduced food intake and the possible development of other deficiencies. Zinc deficiency, which may accompany iron deficiency, can lead to growth retardation in adolescents and may also contribute to the production of some of the "classical" signs of iron deficiency such as koilonychia and Plummer-Vision syndrome.

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III.
ASSESSMENT OF IRON STATUS

An assessment of the iron status of a population is required to determine the need for an intervention program and, where needed, to facilitate the design of the most suitable intervention strategy. Continuing assessment will be necessary to determine the outcome of trial intervention programs and, when regional or national programs are introduced, to ensure their long term effectiveness.

In some countries, sufficient information on the prevalence and causes of iron deficiency already exists to justify the development of an intervention program and to select an appropriate strategy for combatting it. If this information is lacking, a study should be made preferably on random samples of the population. Where this is not considered feasible, studies should be done on those population groups most likely to be at risk, such as preschool children, women of childbearing age and, especially, pregnant women. The status of these groups may be used as an indicator of the iron status of the community.

HEMOGLOBIN AND HEMATOCRIT

Determination of the frequency distribution of hemoglobin concentration or hematocrit values in the population, or a representative subsample, will give information regarding the prevalence of anemia but not the cause. Where anemia is highly prevalent, appropriately designed therapeutic trials (Figure 1) can provide information on the nature of the deficiencies responsible.

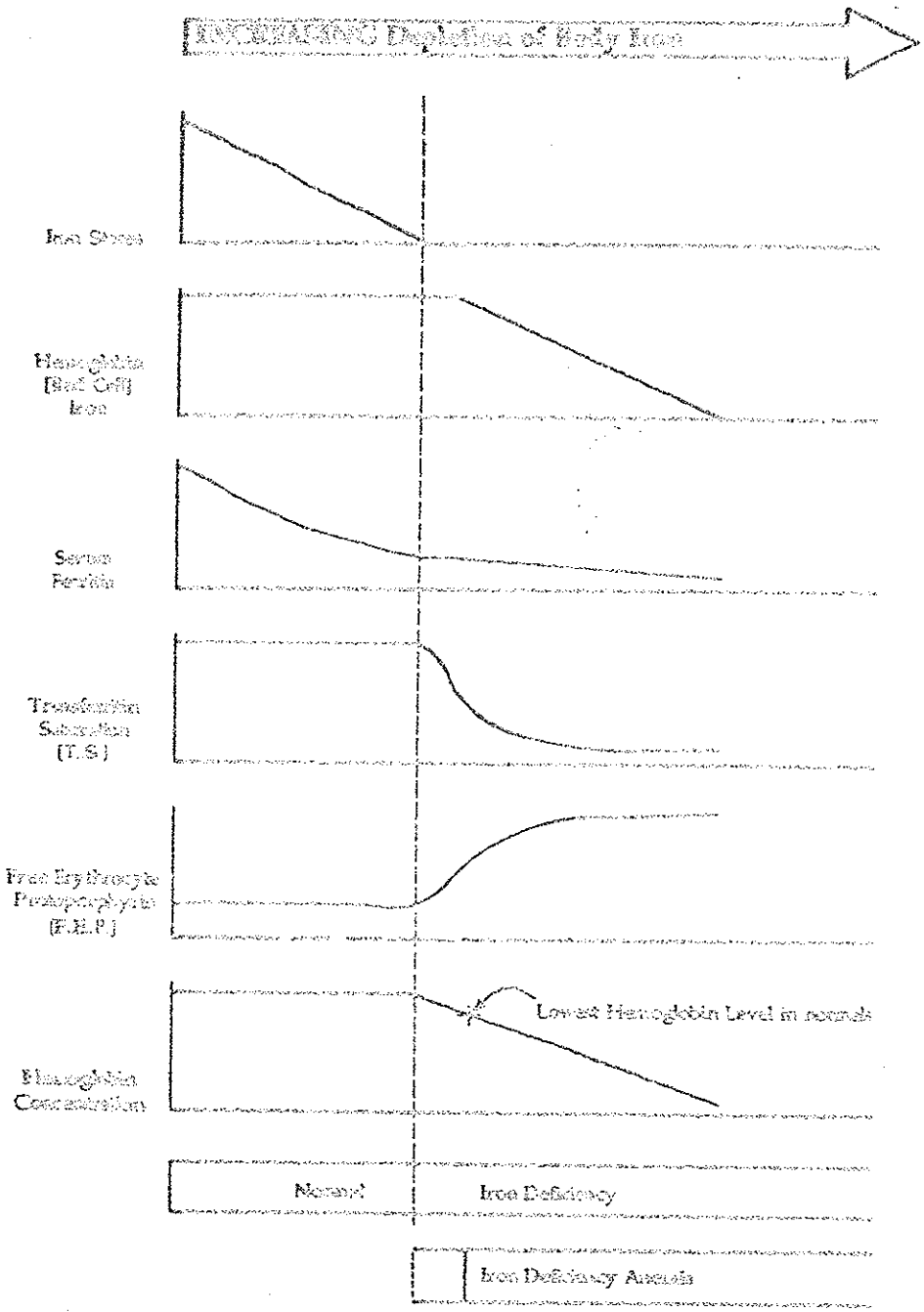
Anemia is the end result of severe deficiency, however, so the hemoglobin concentration and/or hematocrit are relatively insensitive indices of milder degrees of iron depletion. Wherever possible, therefore, employment of other parameters of iron status in addition to the measurement of hemoglobin concentration and hematocrit is highly desirable.

The iron replete adult male not only has a normal hemoglobin concentration but also has iron stores of 500 to 1000 mg. The size of these stores has been assessed in the past through a variety of invasive techniques, such as the histological examination of bone marrow smears for the presence of stainable iron. More recently, however, using immunological methods, it has been shown that small amounts of ferritin are present in the serum (mean normal 70 μg/litre SD ±5 for males and 35 μg/litre SD ±5 for females) which reflect body iron stores. Serum ferritin measurements, therefore, provide a convenient method of assessing the amount of storage iron which can be fairly readily applied to population groups. Phlebotomy studies in normal subjects indicate that on the average a serum ferritin of 1 μg/litre is roughly equivalent to 10 mg of storage iron. With gradual depletion of iron stores, there is a progressive drop in the serum ferritin concentration. It has been suggested that a value below 12 μg/litre represents absence of storage iron.

When iron stores are exhausted and there is a continued negative iron balance, the percentage transferrin saturation with iron falls from an average of above 30% to less than 15%. Since erythropoietic precursors are being deprived of their normal iron supply, not all the available protoporphyrin is formed into heme and as a result there is a concomitant rise in free erythrocyte protoporphyrin to above 70 μg/ml.

At the same time there is an impairment in hemoglobin production which eventually will lead

FIGURE 1



Changes in body iron compartments and laboratory parameters of iron status during development of iron deficiency due to continuous negative iron balance.

to a decrease in hemoglobin concentration to levels below the lowest observed in non-anemic (normal) subjects (130 g/l in men, 120 g/l in menstruating women, and 110 g/l during pregnancy). In subjects with hemoglobin values just below these levels, the actual deficit in hemoglobin iron may vary considerably because of the wide range of hemoglobin concentrations in normal subjects (men 130-170, women 120-160 g/l).

Hypothetically, the initial effect of a normal individual being subjected to a continuing negative iron balance resulting in a gradual decrease in body iron stores would be a gradual decrease in serum ferritin. With continued negative iron balance, the probability will increase that either the transferrin saturation or free erythrocyte protoporphyrin or both will fall outside their normal range. While the hemoglobin will also decrease during this phase, the change may go unrecognized because of the broad range of hemoglobin values in a normal population.

Ideally, all of these laboratory parameters would be more when assessing the iron status of a population. The most important parameters, however, are the hemoglobin and serum ferritin which monitor both ends of the spectrum of iron status. Thus, in a population with a high prevalence of iron deficiency, the most sensitive parameter is the hemoglobin concentration; when iron deficiency is less prevalent, the serum ferritin is most informative. The transferrin saturation and free erythrocyte protoporphyrin give valuable additional information, particularly in populations with moderate degrees of iron deficiency. The collection of blood samples should be carefully standardized with particular reference to the hour of the day at which the sample is obtained, the amount of physical activity of the subject prior to taking the sample, the position of the subject, and the technique used for obtaining the sample. Conditions of transportation and storage of specimens should also be standardized. The subsequent mixing of samples is of especial importance. In longitudinal studies, whenever feasible, samples for a given estimation from the same individual should be stored and analyzed simultaneously.

IV.
SUPPLEMENTATION

INTRODUCTION

Basically, two principal forms of direct intervention are available: "supplementation," the distribution of hematinics (iron and/or folate) in tablet or (in the case of infants and young children) liquid form, and "fortification," where the hematinic is supplied by adding it to some foodstuff.

When there is a high prevalence of iron deficiency anemia in the population, supplementation will be needed to treat the most severely affected individuals. This is the only way to improve iron nutrition status within a reasonable time period. Expediency is particularly important in pregnancy where the objective is to achieve satisfactory hemoglobin levels prior to delivery.

Supplementation programs may be influenced by a variety of factors such as the nature of the diet, the properties of the iron supplement (tablets) used, the prevalence of parasitic infestations (particularly hookworm and bilharzia) local customs and beliefs, and the organization of the health services. For this reason, a program successful in one area may not succeed in another; each program must be carefully tailored to fit the local situation. An approach to the design and the implementation of supplementation programs is discussed below.

Supplementation and fortification programs are not mutually exclusive. Initiation of a supplementation program should not exclude planning an iron fortification program concurrently for the same population. Furthermore, while the emphasis initially may be placed on supplying extra iron to populations suffering from increased blood losses (e.g., hookworm and bilharzia infestation), parallel measures should be taken to reduce the prevalence of anemia more fundamentally by health, education, and socioeconomic reform.

TARGET POPULATION GROUPS

The target population for supplementation must first be identified. In most areas the groups with the highest prevalence of iron deficiency anemia are likely to be infants, children, and women of childbearing age, especially pregnant women.

In many areas of the world, in addition to the normal physiological requirements, increased iron is needed to cover pathological blood losses, especially those due to parasitic infestation, e.g., hookworm and/or bilharzia. In these same areas there is also often a low availability of ingested iron due to the characteristics of the diet. These two factors cause an increased prevalence of iron deficiency which also may affect males. In view of the increasing evidence of the impairment of work output by persons with even mild iron deficiency anemia, those engaged in manual labor, if iron deficient, should also be considered an important target group.

TYPES OF SUPPLEMENTS

The numerous pharmaceutical preparations of iron on the market often differ widely in their elemental iron content, the iron compounds employed, their pharmaceutical properties (such as their disintegration and dissolution rate in the intestine) and their cost.

All readily soluble ferrous iron compounds suitable for oral administration are, in general, equally well absorbed[1] and produce the same type of side effects with similar frequency.[1,2] Ferrous sulphate, one of the cheapest available compounds, is recommended for use in public health programs.

The way in which tablets are manufactured (e.g., the amount of pressure used to form the tablet, the nature of the excipient, and the type and thickness of coating) considerably influence the biological availability of the iron. As there seems to be no fully reliable *in vitro* method, the bioavailability of the iron in the tablets must be studied by performing an *in vivo* trial.

> The increase in plasma iron concentration three hours after oral administration of the tablets to subjects who have fasted overnight should be compared with the rise obtained three hours after oral administration of an equimolar amount of freshly prepared ferrous sulphate solution. The rise obtained with the tablets should be at least 75% of the rise obtained with the ferrous sulphate solution. This test should be carried out on at least ten healthy individuals. Alternate subjects should be given the tablet first and the others the ferrous sulphate solution first. There should be a one week interval between the tests. The dose of iron in the tablets should be between 50 and 150 mg of elemental iron.

While performing supplementation trials, this test should be repeated on all batches of tablets at at least six month intervals. The tablets must be shown by these tests to maintain this degree of bioavailability of their iron during the whole period of their use when stored under the extremes of climatic conditions which may be encountered in the programs.

SIDE EFFECTS OF IRON SUPPLEMENTS

The side effects of therapeutic doses of oral iron fall into two main categories: (a) those related to the upper gastrointestinal tract — nausea, epigastric pain, and vomiting; and (b) those related to the lower gastrointestinal tract — namely diarrhea and constipation. The prevalence of these side effects, especially those arising from the upper gastrointestinal tract, is dose related.[3] All iron compounds appear to produce the same prevalence of side effects for the same amount of available iron.

The prevalence of upper gastrointestinal side effects may be reduced if iron is slowly released in the gastrointestinal tract. There are some slow release preparations on the market in which the bioavailability of the iron appears to be reduced. A slowly dissolving preparation with a high bioavailability of the iron, if associated with a reduction in side effects and if available at a competitive price, might represent a significant advance in therapy enabling appropriate supplementation to be given with a single daily dose when otherwise several doses of a readily soluble iron tablet might have to be given to achieve the same results. For a slow release preparation the above outlined test of bioavailability (e.g., direct comparison of serum increments with those following a solution of ferrous sulphate) is not valid.

Since ingestion of large quantities of iron tablets may produce fatal iron poisoning, especially in children, safety measures should always be taken to minimize this risk.

Theoretically, parenteral iron administration has the important advantages of not requiring the continued cooperation of the patient and of being able to significantly improve iron stores even if the subject is only seen once. The iron in these preparations, however, is complexed with ligands such as dextran or sorbitol, the use of which is associated with the risk of serious and occasionally even fatal side effects. They are, therefore, unacceptable in public health programs even though they may be valuable in the individual clinical situation.

SUPPLEMENT DISTRIBUTION SYSTEM

A major problem with supplementation programs is finding a suitable mechanism for distribution. The methods available for reaching the various target groups are likely to differ from country to country depending on such factors as infrastructure of the health services, population density, school attendance, etc. Methods which have been used in different parts of the world include distribution of supplements to children and pregnant women through schools, antenatal clinics, and maternal and child health centers. Other methods may well be applicable in certain situations, e.g., in industry, agriculture, etc.

PILOT SUPPLEMENTATION TRIAL

When the target population and type of supplement to be employed have been determined, a pilot supplementation trial should be carried out to determine the optimal dose required to produce the desired results.

An appropriate design of the pilot trial can be arrived at after making various calculations as outlined below:

> Amount of Iron to be Absorbed
>
> A calculation can be made of the body's iron requirement in order to compensate for:
>
> - basal iron losses,
> - pathological losses (e.g., due to hookworm or bilharzia infestation),
> - extra demands during periods of growth, pregnancy, and lactation,

- raising the hemoglobin mass to a normal level in anemic subjects, and
- supplying the tissues with sufficient iron to ensure normal storm and physiological function.

Following such estimates, the factor of bioavailability must be considered.

Amount of Iron to be Ingested

Rough calculations of the amount of supplemental iron needed to achieve the desired increment in absorption within a given period of time can be made from available information. Since many factors influence the absorption of both food iron and supplemental iron, a pilot supplementation trial must be made under existing conditions to ensure that the calculations are correct in the local situation.

The pilot trial should be carried out on a representative sample of the population to study the rise in hemoglobin concentration following the administration of doses of iron. At least two dose levels should be tested — one in the region of the estimated necessary daily supplement and the second at least one level above this.

A Practical Example of Dose Calculation in Pregnant Women

Where there is a high prevalence of anemia in pregnant women, supplementation programs must be designed to cure the anemia and meet the extra demands for iron due to pregnancy. For example, if all women with a hemoglobin of 8 g% are to be adequately treated, the following calculations can be made assuming that:

- the women are first seen at 24 weeks of pregnancy,
- supplementation will be given for 100 days, and
- average body weight is 50 kg.

Total amount of iron required:

Basal daily losses 1 mg × 100	= 100 mg
Iron requirements of fetus and placenta	= 250 mg
Iron for expansion of hemoglobin mass during pregnancy	= 500 mg
Iron to increase hemoglobin concentration from 8-12%	= 400 mg
Total iron requirements	= 1250 mg
Daily amount of iron which must be absorbed = $\frac{1250}{100}$	= 12.5 mg

Assuming an average absorption over the 100 days of five percent, a 100 mg supplement must be given two to three times a day to achieve the desired result of an average daily absorption of 12.5 mg of elemental iron.

A Practical Example of Experimental Design of Pilot Trial in Pregnant Women

The following is an example of a pilot trial aimed at pregnant women in whom there is a known prevalence of anemia. Where there are factors which may affect the hematological response to supplementation, such as different ethnic groups or subjects with abnormal hemoglobins, the initial division of women should be made according to these factors. For example, where there is a high prevalence of hemoglobin E, women with this condition should be studied separately from those with a normal hemoglobin type.

Since the expected increase in hemoglobin concentration following therapy is proportional to the degree of anemia, the frequency distribution of the initial hemoglobin concentration should be similar in each treatment group. Subjects should, therefore, be divided into at least two strata (S 1 and S 2) according to their initial hemoglobin concentration.[4] The dividing point should be higher in populations with a low prevalence of anemia. All subjects with hemoglobin below 8% should be excluded and given treatment.

Examples of strata for populations with a high and low prevalence of anemia are:

	High prevalence	Low prevalence
S1	8 - 9.9	8 - 10.9
S2	10 and above	11 and above

Subjects from each of these strata should then be allocated by sets of random numbers to the various treatment groups. A placebo group also should be included.

The nature and dosage of supplement to be given depends on several factors. When folate deficiency is known to be important, all treatment groups should receive folate in addition to iron. If there is a doubt about the role of folate, an additional group should be given maximal iron supplement but no folate to ascertain the necessity for this nutrient in the supplement. The amount of iron to be given will depend on the prevalence and severity of anemia. For example, if a significant proportion of women have a hemoglobin concentration in the region of 9 g%, and they are to be given the supplement for 100 days, they must absorb an average of 12.5 mg of iron per day. This probably requires the administration of 200-300 mg of iron per day in divided doses. To ensure that the tablets are taken, the tablet consumption by each individual must be supervised. Such supervision, however, cannot be done in a practical public health program. To obtain information on the effectiveness of the supplementation under more realistic field conditions, a group should be included in whom tablet consumption is not supervised, but to whom tablets are distributed through the antenatal clinic or other methods of distribution available in the area. Assuming that the study of folate is also desired, the following therapeutic groups should be used:

Group 1 Placebo

Group 2 (100 mg of iron + 2.5 mg Folic acid). Twice daily

Group 3 (100 mg of iron + 2.5 mg Folic acid). Three times daily

Group 4 (100 mg of iron). Three times daily. No Folic acid

Group 5 (100 mg of iron + 2.5 mg Folic acid). Three times daily

In groups 1-4 tablet consumption should be supervised. In group 5 tablet consumption is unsupervised. If supervision three times daily is impractical, in groups 3 and 4, either the morning and evening tablet consumption can be supervised and the one to be taken in the middle of the day given at the time of the morning visit, or the dose size in groups 3, 4 and 5 can be increased to 150 mg of iron + 2.5 mg of folic acid, and the tablets given under supervision twice daily.

The size of the sample needed to produce statistically significant results depends on several factors and is difficult to predict with accuracy. A preliminary analysis of the results may be done at any time without stopping the trial. When the prevalence of anemia is high, a preliminary analysis may give valid information when approximately 50 subjects in each group have completed the trial. When the prevalence of anemia is low, 100 or more subjects may be needed in each group. If preliminary analysis produces equivocal results, the trial must be continued until sufficient subjects in each group have completed the trial.

The results should be analyzed by determining the change in hemoglobin concentration between the beginning and end of supplementation in each individual. Comparison between the groups may be done by comparing the mean change in hemoglobin concentration using the "t-test" (providing the initial distribution of hemoglobin concentration in the different groups was the same) or preferably by comparing the regression line of the change in hemoglobin concentration in relation to the initial concentration in each group.[4]

Interpretation of Results

By comparing the results of groups 3 and 4, the effect of folate can be evaluated. If 3 is better than 4, then the additional benefit is due to folate. A comparison between groups 2 and 3 will give information about size of the iron dose needed for the target population. If the results in the two groups are equal, clearly the amount of iron in group 2 was adequate. However, if group 3 is better than group 2, examination of the frequency distribution of the final hemoglobin concentration values will give an indication of the efficacy of this dose level. If the results are inadequate, a new trial must be designed with a higher intake of iron and/or a longer duration of therapy.

The results in group 5 will permit an evaluation of the effectiveness of unsupervised tablet administration. If the results in this group are inadequate, another trial must be designed adopting one or more of the following procedures:

- develop a different tablet distribution system,
- increase the motivation of the subjects,
- increase the dose size and/or number of doses,
- increase the duration of the supplementation, and
- attempt to improve absorption from the tablets by encouraging women to take the tablets on an empty stomach.

When it is not possible to include a placebo group in the trial, a substitute group receiving a small dose of iron, e.g., 30 mg per day, might be used. However, this will make the difference in response between group 1 and the other groups smaller and will necessitate the inclusion of more women in the trial for the results to have the same statistical significance.

FIELD SUPPLEMENTATION TRIAL

When a pilot supplementation trial has been shown to be effective, a field trial should be carried out utilizing available distribution channels to ensure that the results obtained in the pilot study can be duplicated when applied on a larger scale under more realistic conditions.

REGIONAL OR NATIONAL SUPPLEMENTATION PROGRAM

When a field trial has been successfully completed, a regional or national supplementation program can be designed and carried out. The need for the program must be understood by everyone to ensure its success.

The personnel responsible for the planning of health care and the allocation of funds must fully appreciate the importance of the program and the need for adequate finances.

The public must be educated regarding the deleterious effects of anemia and ways of overcoming it.

The target population groups must understand the benefits that will accrue to them from cooperation in the program and the importance of regular supplementation.

The importance of the program must be realized by medical practitioners and other health personnel, since a program without the understanding and support of the medical profession cannot hope to succeed.

Efforts should be made to develop suitable publicity for the various groups in different countries. In many studies in the past, information, publicity, and motivation have been largely neglected.

Once a regional or national supplementation program has been established, periodic monitoring is essential to ensure the continued effectiveness of the program.

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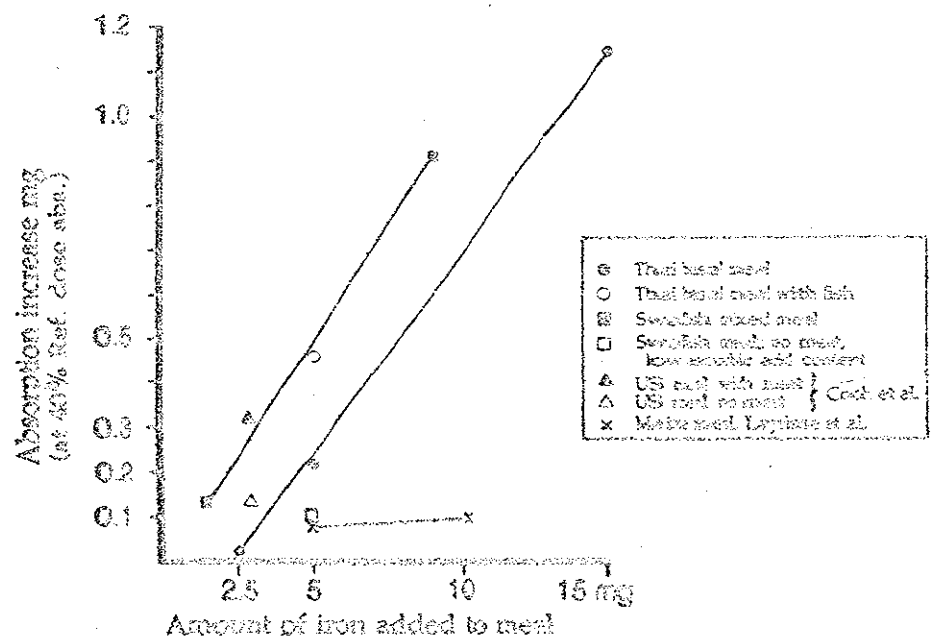
FIGURE II

EFFICACY OF IRON FORTIFICATION
IN RELATION TO PROPERTIES OF MEALS

Comparison of the increase in absorption of iron brought about by different levels of iron fortification added to different types of meals. Results are "normalized" to a reference dose absorption of 40%.[15]



V
FORTIFICATION

Iron deficiency results when the amount of iron absorbed from the diet cannot meet an individual's requirements. Absorption may be limited for one of two reasons: either the total iron content of the diet is too low or the nature of the diet is such that the iron present in the foods is not easily available for absorption. In developed countries, the iron content of the diet is usually low, about 6 mg/1000 calories,[1] but the dietary iron is relatively available; between 5% and 20% can be absorbed by the iron deficient subject. This may be ascribed to 1) the high intake of meat, fish, and poultry which may both be a good source of iron and enhance the non-haem iron absorption,[2] and 2) other substances such as ascorbic acid which enhance iron absorption.[3,4,15] In many developing countries, however, where diets are largely made up of cereals, the iron content may be relatively high,[5,6] since the intrinsic iron present in the food is often fortuitously contaminated with soil iron. Although the iron content of such diets may be high, it is usually poorly absorbed. Isotopic studies have shown that iron absorption is inhibited by a number of substances present in such diets, including phytates, calcium phosphate,[7,9] and tannins, for example, in tea.[10]

The result of a number of studies indicates that when a readily absorbed iron salt is mixed into a meal it forms a common pool with the intrinsic non-haem dietary iron, and its absorption is influenced in the same way by inhibiting or enhancing factors present in the diet.[11-14] This has important implications when setting goals for fortifying a diet (Figure II).

These points underline the importance of defining as precisely as possible the mechanisms responsible for poor iron absorption in a particular population. If the diet is of low iron content, but contains meat and/or fruit, iron nutriture can be expected to be benefited by enriching some commonly consumed item such as flour with relatively modest amounts of iron. If the basic diet is largely cereal-based (especially whole grain cereals), however, iron enrichment may not be effective because of the low absorbability of the added iron. In this situation, other strategies should be explored such as the addition of an agent to promote iron absorption (e.g., ascorbic acid), the removal of an inhibitory agent, or the implementation of a supplementation program.

FORTIFICATION OF THE DIET WITH IRON

Before taking the various steps necessary to implement a fortification program, evaluation of the data provided by prevalence studies and dietary surveys is necessary. Central to this analysis must be confirmation that iron deficiency is the major cause of anemia in the population under investigation. The corollary to this is equally important. Demonstration that anemic subjects will, in fact, respond to oral iron treatment is essential. If, for example, a large proportion of the population is suffering from combined nutritional deficiencies or from malabsorption, fortification trials with iron alone might be unsuccessful. It is, therefore, important to carry out a pilot supplementation trial in which iron is fed to a small group of anemic subjects. Since folate deficiency may also be a complicating factor, comparison of the effects of iron therapy alone with that of iron plus folate in some small segment of the community is advisable. The design of such a pilot supplementation trial is described on pp. 9-11. If the pilot study indicates that iron therapy alone produces a sig-

nificant improvement, a strategy for iron fortification of the diet should be planned. In this context, several factors must be considered:

- a suitable vehicle to which the iron can be added must be chosen,
- a suitable iron compound for addition to the vehicle must be selected,
- the expected levels of iron absorption from the fortified diet in subjects of differing iron status must be demonstrated using radioisotopic techniques,
- results of pilot radioisotopic studies must be confirmed under realistic field conditions,
- if field confirmation is satisfactory, plans for national implementation must be made, with special emphasis on the cost/effectiveness of such a scheme, and
- a system for monitoring the effects of a national program must be devised and implemented. This system should be concerned not only with possible long-term benefits but also with possible harmful effects.

Vehicles for Iron Fortification

The vehicle chosen should be one that is already consumed in adequate amounts by the general population and one that is available for fortification at relatively few production centers so that quality control can be adequately maintained. After fortification, the vehicle should remain palatable and stable, and the added iron should continue to be evenly distributed in the vehicle over long periods of time and under extreme conditions of storage likely to be encountered (i.e., temperature and humidity). Possible vehicles include those discussed below:

Processed Cereals

The major cereal foods, wheat flour, corn meal (maize), and rice, lend themselves readily to iron fortification, especially in countries where these grains are processed through centralized milling operations. While there is good evidence that whole grain cereal products contain substances that inhibit the absorption of iron, the presence of meat or fish in the diet has been shown to partially reverse this effect. The major inhibitors are removed in cereal processing. Cereal products, therefore, represent satisfactory vehicles for acceptable iron fortification in populations consuming Western-type diets.

Salt

Salt is also consumed by all subjects in most population groups. The potential for the use of salt as a fortification vehicle may be limited by interaction with iron compounds and subsequent discoloration and consequent poor acceptance. The relatively small quantities of salt normally consumed in the adult diet (10-15 g daily) also creates difficulties, since it means that the concentration of the fortifying iron compound must be correspondingly high. In addition, most iron compounds have distinctive colors making their presence difficult to disguise. Although these effects are minimized in refined, free-running salt containing desiccants, they pose a major problem in the crude cooking salts widely used in developing countries. Even such salts, however, can be successfully fortified with ferric orthophosphate together with sodium hydrogen sulphate[15] or ascorbic acid.[17,18]

Sugar

In many countries, sugar appears to be suitable for iron fortification.[19,20] It is widely consumed at a level of about 20-100 g daily, it is processed in a small number of places, and it is chemically compatible with a number of iron salts. A major disadvantage to adding ionizable salts to sugar, however, is the precipitation of tannins in tea.

Infant Foods

Many cereals and milk powders for infants are routinely fortified with various forms of iron. The bioavailability of such iron is strikingly improved when ascorbic acid is present.[1] (A ratio by weight of at least 1:5, iron to ascorbic acid, is recommended.) Many infant foods often contain ingredients such as barley flour, eggs and bananas which are known to discolor in the presence of certain iron salts.

Beverages

The variety of beverages consumed throughout the world should not be overlooked as potential vehicles for iron fortification since they are generally consumed by identifiable population segments. For example, tea and coffee are normally consumed by adults; milk is normally consumed by infants and children; juices and juice drinks may be consumed by all segments and, especially, by adolescents. The fortification of beverages requires a soluble iron form that is compatible with all the beverage components and characteristics. Obviously, the predominant beverage flavor must remain unaltered. Many problems related to the iron fortification of beverages can be controlled by the choice of an oxygen impermeable packaging system.

Others

In any given culture or country, a regional food such as fish sauce[21] or a condiment such as monosodium glutamate may be consumed in sufficient quantities by a significant portion of the population to warrant consideration as a possible vehicle for iron fortification.

It is possible that no single vehicle may be found which is both suitable for fortification and consumed in adequate quantities by most of the target population. In this case, more than one food may be fortified if dietary surveys show little risk of excessive iron intakes by population groups who consume both vehicles in significant amounts.

TABLE I

TABLE OF COMMERCIALLY AVAILABLE IRON COMPOUNDS (JUNE 1977)

KEY:

G = Good, F = Fair, P = Poor.
— = Information not available

R = Recommended, V = Variable,
NR = Not Recommended

Relative Cost Factor:
$\frac{\text{\% iron content}}{\text{price}}$ x Bioavailability factor in humans

Bioavailability factor: G = 1, F = 2, P = 3

	% Iron Content	Bioavailability in Humans	Bioavailability in Animals	Common Vehicle: Processed Cereals	Common Vehicle: Salt	Common Vehicle: Sugar	Common Vehicle: Infant Foods (milk)	Common Vehicle: Beverages	Relative Cost Factors: x	U.S. Prices (Sept June 1977) Iron component: x
Soluble Iron Compounds										
Ferrous Sulphate	20.1	G	G	V	V	R	V	R	3.1	0.65
Ferrous Citrate	21.3	G	G	V	V	R	V	R	4.3	7.88
Ferrous Succinate	32.9	—	G	V	NR	NR	R	—	—	2.35
Ferrous Gluconate	11.5	—	G	V	V	R	R	R	—	3.41
Ferrous Glycinate	23.9	G	G	—	NR	NR	V	R	4.3	3.63
Ferrous Lactate	20.2	—	G	—	—	—	—	—	—	3.35
Insoluble Iron Compounds										
Ferric Citrate	20.4	G	G	NR	NR	NR	NR	NR	2.9	2.48
Ferric Sodium	27.9	—	G	NR	NR	NR	NR	NR	—	1.86
Ferric Pyrophosphate	11.0	—	P	R	NR	R	R	V	—	—
Ferric Ammonium Citrate	17.9	G	P	V	NR	NR	R	V	5.1	3.06
Ferric Orthophosphate	18.7	G	G	V	NR	NR	V	V	5.6	12.96
Insoluble Iron Compounds										
Ferric Orthophosphate	28.6	F	P	R	R	R	R	V	7.0	1.72
Ferric Oxide	69.9	F	P	NR	NR	NR	NR	NR	4.3	2.06
Elemental Iron										
a. Reduced by Hydrogen (99.8 Fe pure)	98.5	—	F	V	NR	NR	NR	NR	2.1	1.86
b. Reduced by Carbon Monoxide	98.0	—	F	V	NR	NR	NR	NR	—	1.53
c. Carbonyl Iron	98.0	—	F	V	NR	NR	NR	NR	—	3.06
d. Reduced by Electrolysis (99 pure)	97.0	G	G	V	NR	NR	NR	NR	1.0	3.06
Ferric Pyrophosphate	25.0	P	P	NR	NR	NR	NR	NR	4.8	—
Ferric Citrate	36.3	P	P	NR	NR	NR	NR	NR	8.6	—
Ferric Sodium	36.0	P	P	R	R	R	R	V	10.1	—
Ferric Pyrophosphate	36.0	P	P	R	R	R	R	V	16.1	1.92
Sodium Iron Pyrophosphate	16.0	P	P	R	R	R	R	V	16.1	1.92
Iron Complex Compounds										
Sodium Ferric EDTA	13.0	G	G	V	—	R	V	V	7.7	2.86
Ferrochelate	14.0	—	G	—	NR	NR	—	—	—	—

Total evaluation requires cost analysis. Normalize Bioavailability, multiply the relative cost factor times the price per kilo of iron compound. Correct iron content per kilo should be used when available.

Such an approach would be particularly useful where there are marked differences in dietary patterns in different ethnic groups or in people in different geographical regions.

Still another approach is the introduction of a new type of food as the iron vehicle. Because of the difficulty of changing dietary habits on a large scale, this technique is most likely to be effective with small target populations such as preschool children, pregnant women, etc. In these cases, introduction of the product should be accompanied by concentrated educational and promotional programs to stimulate consumption.

THE CHOICE OF A FORTIFYING COMPOUND

As mentioned above, there are three options for increasing iron absorption by fortification. The first and most obvious is to add an absorbable iron salt to some vehicle in the diet; the second is to add some facilitator of iron absorption such as ascorbic acid; and the third is to do both. All three approaches have been shown by radioisotopic studies to be feasible.

In considering *iron compounds* it is essential to review not only the chemical and physical properties of the compound itself but also those of the vehicle to be fortified. Unfortunately, many iron compounds, especially those most readily absorbed, are highly reactive and produce a variety of undesirable changes in foods to which they are added. The following are examples of the chemical properties of iron compounds that must be kept in mind:

- ferrous salts may be oxidized to form yellow, green, or black ferric oxide,
- iron salts may react with phenolic compounds such as tannins and propyl gallate to form blue-black colors,
- iron compounds may react with sulphur compounds to produce a black color,
- iron compounds may increase the activity of oxidation enzymes that cause off-colors, -odors, and -flavors,
- iron is a known pro-oxidant and an iron compound may catalyze the development of oxidative reactions,
- high density products such as reduced iron powders may require special measures to achieve a stable and uniform distribution,
- the color and flavor of the iron compounds themselves may be undesirable and carry through into the food. These problems may be especially noticeable in iron-fortified beverages, and
- the solubility characteristics of the iron may not be compatible with the food to be fortified.

CURRENTLY AVAILABLE COMPOUNDS

A list of currently available iron compounds that have either been used in fortification programs, or that can be considered for use are set out in Table I. The table includes the soluble ferrous and ferric salts, the insoluble iron compounds, and complex compounds. Those compounds that have been added to food and tested by radioisotopic means in human subjects have been designated. The bioavailability of such compounds, as judged by animal studies, has also been included although there are limitations in relating such data to humans. The table also indicates possible vehicles for iron fortification and the degree to which different iron compounds react with such vehicles.

The extent of the problems created by the chemical and physical properties of particular compounds is dependent in part on the conditions of processing, storage, and distribution. Many of the chemical and enzymatic reactions previously mentioned take place rather slowly or can be retarded by appropriate storage conditions. If the food product is to be consumed within a short time after preparation, a soluble form of iron may be used that would be completely unsatisfactory in a food requiring lengthy storage under adverse conditions. For example, ferrous sulphate is a suitable fortificant for flour if the flour is to be used within a period of weeks. If, on the other hand, it is to be stored for extended periods, rancidity may result.

At the present time, metallic iron powders (reduced iron, carbonyl iron, and/or electrolytic iron), ferrous sulfate, ferrous fumarate, ferric orthophosphate and ferric pyrophosphate are the most commonly used forms of iron for food fortification. While ferrous sulfate is one of the least expensive iron salts, it is also one of the most chemically reactive, thus limiting its use in many foods. Reduced iron powders, which are insoluble except at low pH, are chemically inert and inexpensive. Their absorbability varies widely depending on the pH achieved during processing, on the particle size or, more probably, on the surface area per unit weight.

Evidence from radioisotopic studies in man indicates that the absorption of iron from salts, such as ferrous sulfate, ferrous fumarate, ferric chloride,

and ferric glycerophosphate, is similar. Two laboratory-produced ferrum reductum products have also been shown in man to be absorbed to the same degree as ionizable iron salts.[22,23] Whether this is true of commercially available iron powders (reduced iron, carbonyl iron and electrolytic iron) is not known, although studies in rats and *in vitro* indicate that many of these products may not be as well absorbed as are the readily soluble iron salts.

Ferric orthophosphate and sodium iron pyrophosphate have been shown not to form a common pool with the non-haem iron present in food and are poorly absorbed.[22] The bioavailability of the iron in ferric orthophosphate has been reported to increase when fed together with sodium hydrogen sulfate.[16]

Sodium iron EDTA may have advantages as an iron fortificant. It is stable under usual conditions of storage, it exchanges completely with the non-haem iron food, and it may even enhance absorption of the non-haem iron present in a meal.

Haem iron, because of the high bioavailability when given in small amounts,[24] has been suggested as a possible fortification agent. The feasibility of producing a dried haem product derived from slaughtered livestock is currently being explored.

Another approach is the use of a facilitator of iron absorption such as ascorbic acid. When it is given in combination with iron salts, absorption of iron from the diet is significantly enhanced.[3,17] There are, however, technical difficulties in adding both agents to vehicles such as salt and sugar. Ascorbates are relatively unstable, and the ascorbic acid may have other effects.

Meat is the only other facilitator of non-haem iron absorption that has been studied in detail.[3] While the addition of meat to national diets would be expected to significantly decrease the prevalence of iron deficiency, its expense precludes its use as a practical solution in most developing countries.

Pilot Fortification Trial

When a form of iron and the vehicle for fortification have been chosen, a radioisotopic absorption study is needed to obtain information regarding the availability of iron in the basic diet and the degree to which iron absorption is likely to be modified by the proposed fortification. These trials involve the use of two isotopes of iron in each experimental subject. Absorption is calculated from the percentage of radioactivity present in the blood two weeks after oral administration of the isotopes. In such studies a standard meal typical of that consumed in the community is eaten on the first day of the study. The non-haem iron pool in the diet is labelled using a radioiron tag (^{59}Fe or ^{55}Fe). On the next day the same meal is fed, but the fortifying iron is added, having been labelled with the other isotope of iron.* In this way, it is possible to establish to what extent, if any, absorption was increased by the dietary manipulation.[25] In such studies, the subjects act as their own controls, thus minimizing difficulties due to wide variation in iron status and, concomitantly, iron absorption.

When conducting such studies, the absorption of a small dose of iron (3mg) given as ferrous ascorbate to the same individual at the end of each food iron absorption experiment should also be reviewed. This determination provides an index to the avidity with which subjects absorb iron and is an indicator of their iron nutriture. Such information makes possible meaningful comparisons between individuals or groups of differing iron status. Ten to twenty subjects must be included in studies of this type because of the day-to-day variations in absorption. A number of trials may be necessary before a dose of iron and/or facilitator is identified which appears effective for implementing the fortification program.

Knowledge of the prevalence of anemia in a given population should permit the prediction of the type of benefit that might be expected to accrue from the chosen fortification program (Figure III).

FIELD FORTIFICATION TRIAL

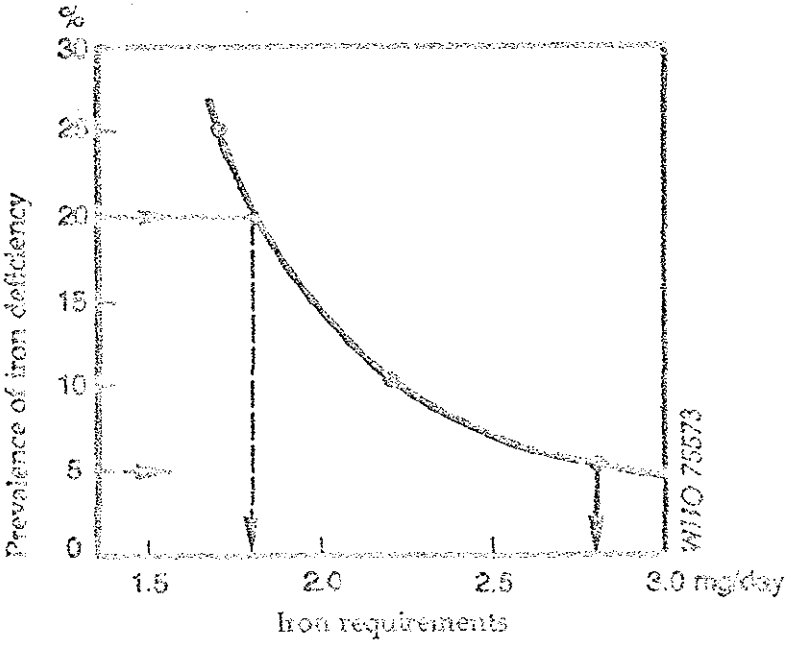
When a suitable iron compound and vehicle have been identified and pilot studies have indicated adequate availability of the fortification iron, a field trial should be carried out.

A number of factors should be considered in the design of a field trial, such as:

- the prevalence and severity of iron deficiency, e.g., an iron deficient population will show a greater response than will a population with larger iron stores,
- the proportion of people in the population with increased iron losses. These subjects will respond more slowly,
- level and type of fortification iron,
- laboratory parameters studied and the accuracy and precision of the methods and procedures (see Chapter III),
- sample size, and
- duration of the study.

*This technique can only be applied when it is known that all the fortification iron forms a part of the non-haem iron pool. If this is not so, the bioavailability of the added iron must be determined by measuring absorption from the meal and from the fortificating compound separately and simultaneously.

FIGURE III
PREDICTION OF THE EFFECTS OF FORTIFICATION ON THE PREVALENCE OF IRON DEFICIENCY



The effects of fortification can be predicted from the known distribution of iron requirements in women and the measured increases in iron absorption from typical meals at different levels of fortification. The increase in absorption required to achieve a certain effect can also be calculated. Thus, if the mean absorption of iron is 1.8 mg/day the prevalence of iron deficiency will be 20%. Increasing this absorption by 1 mg/day will reduce the prevalence of the deficiency to 5% of the population.

The sample size and the duration of the study will be dependent on the other factors and must be adjusted to give statistically valid results. Normally such a trial would need to last at least two years.

The trial should involve both the test group and at least one control group which receives the unfortified vehicle in place of the fortified one.

The initial sample size should be large enough to ensure adequate numbers at the end of the trial. Because of population mobility and other causes, a variable dropout rate of subjects per year of study must be anticipated. If available, data regarding dropout rates in similar long-term trials in the community may be used for estimating the expected dropout rates during the duration of the fortification.

Since considerable amounts of the fortified vehicle will be needed, quality control of the product is necessary to ensure that it is of uniform standard throughout the trial. Periodic random checks of iron content should be made on samples from the site of production, distribution centers, and individual homes. Control of the distribution of the fortified vehicles and regular estimates of individual or at least family consumption and acceptability of the product are essential.

The timing of blood sampling and other field measurements should be determined at appropriate intervals as suggested by the data derived from the simulated fortification trial and by other factors, such as seasonal dietary variations, morbidity, changes and other sociocultural influences.

The cooperation of the population must be ensured and promoted throughout the duration of the study. The purpose of the trial should be carefully explained to the participants. The personnel conducting the trial should be directly involved in the

health services to obtain better collaboration and to ensure that inappropriate iron therapy is not given.

Any response to fortification must be compared with the changes occurring in the control population to ensure that the observed changes are due to the intervention and not due to some other factor common to both the test and control groups. As iron deficiency improves, deficiencies in other hematopoietic substances (folate, in particular) may become evident.

As is apparent from this discussion, fortification strategy will vary according to the particular need. In developed countries, where iron content of the mixed diets consumed is often low, any of a variety of simple iron salts or readily absorbable powders would be expected to be beneficial. In developing countries, however, where cereal diets contain large amounts of inhibitors, this approach may be insufficient, and the additional use of some absorption enhancing agent might be required.

PLANNING FOR NATIONAL IMPLEMENTATION

Once the required scope of the fortification program has been established and its feasibility has been demonstrated in a simulated fortification trial, planning for national implementation should begin and be closely coordinated with subsequent steps in the development of the program.

Several points merit special consideration:

- Government regulations may have to be established and/or revised before the program can be implemented.
- Liaison with appropriate agencies should be established and/or revised to develop a workable scheme for implementation, regulation, and enforcement of the program.
- Methodology, standards, and testing procedures must be established to ensure that the appropriate fortification iron is added at the specified concentrations. This is especially important as iron salts may show unexpected batch-to-batch variations.
- Periodic nutrient absorption tests may also be advisable because seemingly minor changes in production procedures over a period of time may change absorption characteristics.
- Estimates of capital expenditures and operating costs should be made as early as possible in the program to ensure the availability of adequate funding to implement and support the program. If funds are inadequate for the optimal program, plans can be adjusted at an early stage to curtail the scope of the program and concentrate on the most critical objectives. Estimates of capital expenditures should include: a) a projection of production requirements several years into the future; b) a survey of existing production facilities to determine their suitability and available capacity for the type of product being developed; and c) an estimate of expansion and modifications required.
- Estimates of operating costs can be made early in the program but must be updated repeatedly throughout the development of a commercially feasible production process.
- A cooperative program should be established with appropriate technical groups to ensure that the products and processes developed are optimal from both nutritional and manufacturing viewpoints. Factors to be considered in developing a commercial process should include: a) the availability and cost of raw materials; b) uniform distribution of the iron at the specified levels; c) adequate control procedures to ensure that the product meets specifications; d) quality of the product; and e) total production costs.

The government or organization sponsoring a food fortification program must maintain control over the food processing companies participating in the fortification program. The responsibility for the type of iron compound and the level of iron added must be guaranteed by the promulgation of minimum specifications agreed to and accepted by both the regulator and the regulated. Procedures to enforce compliance must also be established and understood by both parties. Failure to establish acceptable specifications and/or enforcement procedures by countries attempting a fortification program eventually results in distrust, dissatisfaction, and a discontinuation of the program.

Consideration should also be given to conducting acceptance studies in which a representative population is offered the fortified food on a free-choice basis under the same conditions as are planned for the final program. These individuals should not be included in the nutritional evaluation or offered an incentive that would not be part of the planned program. The results of the acceptance study will indicate whether or not a consumer education program will be necessary or helpful in implementing the program. If acceptance is very poor, some type of financial subsidy for target groups may be required, or a search for a more acceptable vehicle and/or iron source may even be necessary.

MONITORING AND EVALUATION

Once an information program has been initiated on a continuing basis, a monitoring and evaluation program should be established to ensure that objectives are being met. This program should consist of periodic field studies (using the techniques and procedures described previously) to measure the iron status of the population. An effective monitoring program will serve the following purposes.

- During the earlier phases of the program it will determine the degree to which the program is achieving its objectives. Satisfactory results will provide justification for continuing the program, and more importantly, poor results will signal the need for modification of the program.
- It will identify any population groups not responding satisfactorily that may require special programs such as supplements in addition to fortification.
- Most successful fortification programs will unavoidably increase iron absorption in non-target population groups which already have adequate iron stores, such as adult males. The monitoring program should also include a representative cross section of such subjects and also individuals with known abnormalities of iron absorption such as occur in hemochromatosis, thalassemia, and in some alcoholics. Such monitoring programs should be considerably facilitated by the use of serum ferritin measurements to quantitate body iron stores.

V.
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VI.

FOLATE

REQUIREMENTS

In addition to iron, many other nutrients are necessary for normal hemopoiesis. From a public health standpoint, however, folate is the only other hemopoietic nutrient of wide importance.

For a variety of reasons, knowledge regarding folate requirements is not as precise as in the case of iron, and the techniques available for measuring the absorption of folate are relatively crude. A 1972 report of a WHO Expert Group[1] estimated that adults need 400 μg of folate* per day in their food. Because of the increased requirement in pregnancy, the recommended intake[1] was increased to double this amount (800 μg per day). Folate deficiency is most frequently found in pregnant women.

The earlier 1970 lower estimates of requirements by a joint FAO/WHO Expert Group[2] were the basis for the recommended intake levels of 200 μg/day for adult men and women and 400 μg/day for women during the latter half of pregnancy and lactation published in 1974 by WHO and FAO.[3]

The Food and Nutrition Board in 1974 adopted as Recommended Dietary Allowances[4] the same higher levels (400 and 800 μg) as recommended by the 1972 Group.[1] An extensive review of evidence concerning folic acid in relation to human nutrition requirement has recently been published by the Food and Nutrition Board.[5]

ASSESSMENT

The most convenient method for assessing folate status is the measurement of serum and red cell folate concentrations by microbiological or radioisotopic dilution assay. Serum concentrations reflect recent dietary intake while red cell concentrations change more slowly and reflect dietary intake over longer periods of time. Serum concentrations below 3 ng per ml and red cell concentrations below 100 ng per ml are considered to indicate deficiency.[1] Red cell concentrations of folate may be deceptively high in the presence of iron deficiency.

The final proof of folate deficiency is the ability of supplemental folic acid to produce a hematological response.[6] Wherever possible a therapeutic trial should, therefore, be conducted to confirm the diagnosis of folate deficiency. The principal of the design of such a trial is similar to that outlined in Chapter IV, pp. 9-11. The results are monitored by studying the response of hemoglobin concentration or hematocrit together with measurements of serum and red cell folate concentrations.

INTERVENTION

Where folate deficiency is shown to be a significant cause of anemia, either *per se* or in association with iron deficiency, steps should be taken to deal with the situation. The most frequently used intervention technique is therapeutic supplementation which is widely practiced in antenatal clinics in many parts of the world.

It has also been suggested that folate fortification of selected foods may be useful in certain population groups most at risk from folate deficiency.[7] The bioavailability of folic acid added to maize or rice was estimated by comparing the rise in serum folate levels after administration of a single dose of 1 mg folic acid administered either in the form of enriched food or as the folic acid solution alone.

*Measured as "total" folate including oligo and polyglutamate forms.

By this method the availability of folic acid was found to be 53 percent in maize, (range of 32-77 percent), 58 percent in rice, and 38 percent in bread baked for one hour. Maize appears to be a particularly suitable enrichment vehicle.

A pilot field trial in which folic acid-enriched maize was used under home conditions demonstrated the practical feasibility of such a program in raising red cell folate concentrations.[7] The amount of folic acid that prevented folate deficiency in pregnant subjects in this population group was found to be 400µg per day and enrichment at this level has been recommended.[8] This amount of folic acid poses no hazard to patients with undiagnosed vitamin B_{12} deficiency.

VI.
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VII.

SELECTION OF INTERVENTIONS: A NATIONAL STRATEGY FOR CONTROL OF IRON DEFICIENCY ANEMIA

An intervention program for a given country can be selected only after assessing the extent and severity of iron deficiency, the factors responsible for the deficiency, and any relevant coexisting deficiencies. Furthermore, the precise strategy selected may vary somewhat from country to country, depending on the relative priority given by responsible officials to iron deficiency in relation to other health needs and the available resources of personnel and finance.

The two possible direct methods of intervention are supplementation and fortification; additional interventions that may complement these are food and nutrition education and parasite control. These intervention strategies differ in the time required to achieve desired benefits, in initial and continuing costs, and in other requirements and effects. These are summarized in *Table II*.

DEFINITION OF THE PROBLEM AND GOALS

The accompanying scheme for the control of nutritional anemia (Figure IV) outlines the planning steps necessary to develop appropriate strategies to combat iron deficiency. The first such step is the definition of the problem, i.e., obtaining an estimate of the prevalence of iron deficiency anemia or of the nutriture of the population. The estimate of the presence of low, medium or high prevalence of severe, moderate, or mild deficiency determines which type of intervention is most appropriate.

In many countries, information on dietary intakes and on the prevalence of nutritional anemia and deficiencies of hemopoietic nutrients is available. In other countries, however, such information is lacking and should be obtained. The procedures for collecting needed data have been discussed in Chapter III.

Although hemoglobin concentrations of less than 13 g/100 ml of blood in adult males, 12 g/100 ml in non-pregnant women of childbearing age, and 11 g/100 ml in pregnancy have been suggested as levels indicating anemia, this is an oversimplification. For example, even in a well nourished, healthy population a small proportion of subjects will have a hemoglobin concentration below these values, while other individuals with a higher hemoglobin concentration may have suboptimal hemoglobin levels as indicated by an increase in hemoglobin following therapy. A more scientific approach to determining the proportion of the population likely to be suffering from anemia at any given hemoglobin concentration is to compare the observed frequency distribution curve with the frequency distribution curve of known normal hemoglobin concentrations. Whichever approach is used, minimal acceptable standards should be set in each country. Goals may be expressed in terms of either the acceptable proportion of individuals having hemoglobin concentration below a certain level, or the acceptable frequency distribution of hemoglobin concentrations within physiologic groups.

In countries or regions where there is a low prevalence of anemia, an estimate of the percent of the population with latent iron deficiency or low iron stores (refer to Figure I in Chapter III) may be more meaningful. This may be estimated by determining the frequency distribution of indicators of iron stores in the population. Again the goal to be achieved can be defined as the acceptable percent-

age of the population with low iron stores (e.g., serum ferritin of less than 12 mg/l). Whether hemoglobin or other indices of iron nutriture are employed, the higher the standards set, the longer and more costly the program may be.

If the prevalence of anemia and/or nutritional deficiency is low, general public health action may not be required. Even so, studies on very high risk groups, such as pregnant women or 1-3 year-old babies, may reveal needs for supplementation to meet the extra requirements of these groups.

A high prevalence of anemia or nutritional deficiency calls for some form of intervention. The precise form of intervention strategy selected will depend on a number of considerations, such as the urgency of the problem compared with other pressing health problems and the available financial, personnel, and technological resources of the country. The strategy may well include a combination of such measures as remedial and preventive supplementation of groups at highest risk; enrichment or fortification of food designed for use by specified target groups, and/or fortification of an appro-

TABLE II
CONSIDERATIONS IN SELECTION OF INTERVENTION PROGRAM FOR CONTROL OF IRON DEFICIENCY

Type of Intervention	Population Coverage	Time required to achieve benefit	Focus	Initial Costs	Continuing Costs	Public Participation	Personnel Requirements	Degree of Preventive	Initial Effect	Continued Effect	Complexity of Monitoring
Supplemental Iron	Individual	Relatively short (months)	Single or multi-nutrient	H	H	VA	H	L	H	H	D
Fortification	General or target population	Medium (1-2 yrs)	Single or multi-nutrient	M	L	N	L	H	M	L	S
Food-Education	General population	Long (years)	Multi-nutrient	M	M	A	V	H	H	M	D
Socio-Economic	General population	Long (years)	Multi-nutrient	V	V	A	V	H	V	V	V
Parasite Control (Hookworm)	General population	Long (years)	Single nutrient multi-factored	H	H	VA	H	M	H	H	S

KEY
A — Active
D — Difficult
H — High
L — Low
M — Medium or Moderate
N — None
S — Simple
V — Variable
VA — Very active

priate generally used staple foodstuff; educational programs; and/or other public health measures aimed to reduce parasitism and improve maternal and child health or other relevant conditions.

SUPPLEMENTATION STRATEGY

When there is a high prevalence of anemia, a therapeutic supplementation program is indicated initially to deal with the situation, because fortification alone will not correct iron deficiency anemia quickly enough.

The iron is administered in the form of a tablet, capsule, or elixir. Because multiple daily doses are often required, it may be inconvenient for the consumer and may pose problems of ensuring regular intake. The oral iron may also produce various side effects. Nevertheless, relatively large amounts of biologically available iron can be administered by this method so that benefit can be obtained in a relatively short period.

At the same time as supplementation is undertaken, the possibility of also pursuing a fortification program should be examined and, if feasible, should be implemented. As the prevalence of anemia is reduced following successful supplementation, fortification may be adequate to maintain the nutriture of the population except among special groups such as pregnant women with very high requirements for iron.

Supplementation generally is limited to a selected group or groups of the population where distribution on an individual basis is possible. Supplementation has a relatively high per capita cost because of the expense of the iron preparation and distribution programs. The latter can be minimized by utilizing existing organized group contacts — accordingly, supplementation programs are frequently tied into clinical health care programs. Programs of supplementation should be coordinated within the prevailing health systems of the country and monitored to assess their effectiveness. Governments should be fully informed of the results.

Because supplementation often focuses primarily on the pregnant woman, the possibility of a folate deficiency should also be considered and combined iron and folate supplementation may be necessary (see Chapter IV).

FORTIFICATION STRATEGY

Since effectiveness of fortification is not realized until significant time has elapsed, programs should be planned on a long-term basis. A fortification program provides a daily increment to the food iron supply through the least expensive, most consistent, and least obtrusive of methods; can reach the largest number of people with a relatively small effort and, if correctly planned and conducted, is well accepted. Since food habits are difficult and slow to change, food fortification is the most direct and efficient approach to increasing dietary intake of iron. Such programs may be directed either at whole communities in which the prevalence of deficiency is high throughout the community, or at vulnerable population groups that can be reached through particular foods — for example, infants who in some countries can be reached by fortification of processed baby foods.

Iron can be an adjunct fortificant by including it along with other nutrients in a single mixture. When so combined with other nutrients in an enrichment process, the delivery costs for iron become exceedingly small, and the potential for multiple upgrading of the nutriture of the population is great.

Before initiating an iron fortification delivery system, an iron compound suitable for use and an appropriate food vehicle must be selected. The problems and considerations regarding these factors are described in Chapter V. The food vehicle selected must be one that is generally consumed in reasonably constant quantities throughout the population, is processed in a few central plants, does not show wide fluctuations in price, is purchasable by all persons, is a food in which the fortificant is chemically stable and from which it has acceptable bioavailability. Production cost estimates should include manufacturing, requisite packaging, quality control, adjusted distribution, and new tariffs (if levied). Income from sales and potential market expansion should also be estimated. Other factors to consider are government subsidy, industry absorption of fortification costs, and influence on the cost or price to the consumer. Consumer costs must be kept to a minimum to encourage consumption of the vehicle. The government should be made aware of the benefits of iron fortification so that proper regulations, controls, and support will be developed.

Any fortification program must be evaluated for its effectiveness to ensure that it meets the intent of the government and industry in improving the nutriture and health of the population. To do so, a surveillance system should be established to monitor the iron status of the recipient population. Iron fortification should increase hemoglobin and

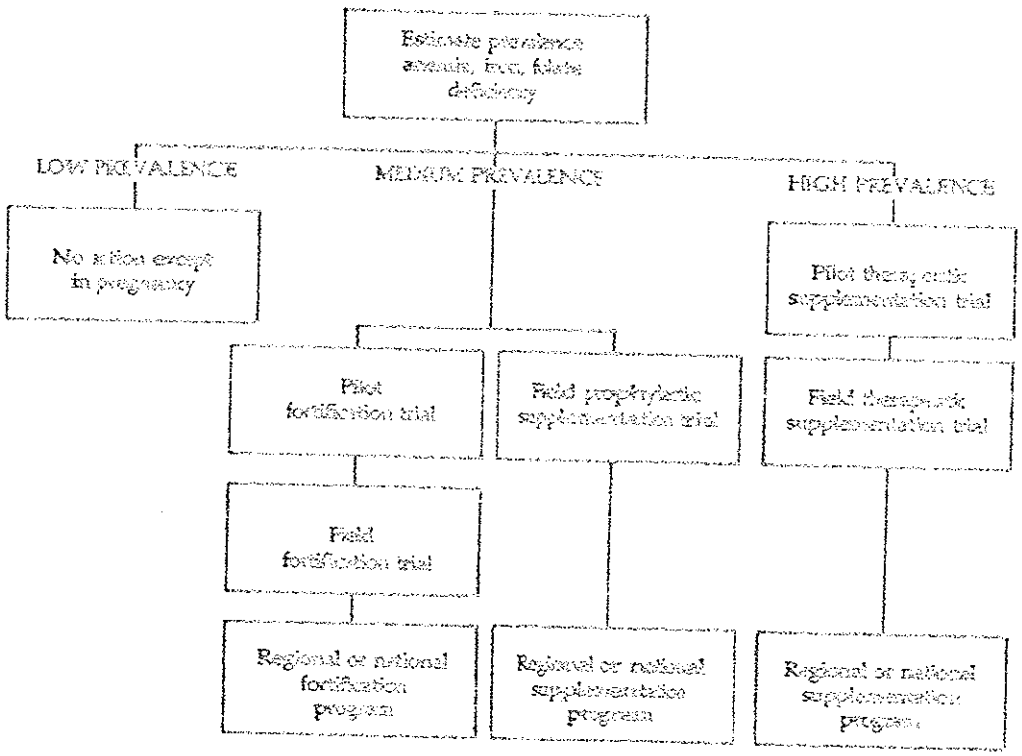
iron stores in most cases of mild to moderate deficiency. Under circumstances of moderate to severe anemia, which may be complicated by parasitic infestation or pregnancy, supplementation with iron may be necessary to correct the deficiency. Accordingly, a program of supplementation should be considered first and fortification as an accompanying intervention.

PARASITE CONTROL

In many areas of the world, iron deficiency anemia is aggravated by increased blood loss due to parasitic infections, especially hookworm and bilharzia. Increased dietary iron intake can balance only mild to moderate blood losses; continuous iron supplementation is needed where heavy infestations result in continuous or repeated blood losses. The permanent solution to this problem, the eradication of the parasites, is a difficult procedure involving:

a) effective treatment of the host,
b) protection of individuals from reinfestation through wearing of footwear to avoid expo-

FIGURE IV



Scheme for the control of Nutritional Anemia. Each step should be successfully completed before proceeding to the next one. If a given trial is unsuccessful, it must be redesigned and the step repeated.

sure to hookworm infection or avoiding exposure to bilharzia contaminated waters,

c) the construction and use of proper latrines, and

d) molluscacidal treatment, where relevant

A parasite eradication program requires years and even decades of persistent efforts; reinfestation may result from any relaxation of control. Complete eradication may in fact be unattainable and the goal of the program may need to restricted to control of the infestation. Maximal success of control programs occurs when the overall socio-economic environment of the infested population is significantly improved. In the meantime, however, alleviation of iron deficiency can be attained by increasing the iron intake through supplementation and fortification, and thereby improving the health and productivity of the population despite some continuing infestation.

FOOD AND EDUCATION

While stress has been laid on fortification and supplementation, dietary modifications can increase intakes of available iron and folate and of enhancers of iron absorption such as meat and fish and vitamin C-rich fruits and vegetables. In less developed countries, foods that facilitate iron absorption such as meat, poultry, and fish are not available to the general population due to scarcity, poverty or dietary practices. In developed countries, iron-rich foods frequently are not consumed in adequate amounts by segments of the population. In either the developed or developing countries, adequate educational programs can do much to alleviate the iron deficiency. To be effective, efforts must address not only the nutritional properties of foods and nutrient needs, but also the cultural role of foods and attitudes toward them. Simple principles of hygiene and health must be taught and basic understanding of cost values of foodstuffs given. Supplementation, fortification, and parasitic control programs often may serve as motivational stimuli for interest in nutrition and health education. In developing countries or among low economic groups, economic improvements may be a prerequisite to permanent alleviation of malnutrition. Changes in socio-cultural attitudes often are desirable, although these changes, particularly socioeconomic changes in developing countries, do not occur over a short time; nevertheless, a national program to combat iron deficiency anemia must include such objectives.

Educational efforts concerning selection, production, and consumption of foods may be modified to include information on the relevant material such as environmental sanitation and personal hygiene. Education of parents on the benefits of spacing of birth and the special needs of young mothers can help reduce the anemia problems. These efforts should be included in the total educational program, whether administered within agencies responsible for health, agriculture, or education.

A well nourished and healthy individual is the ultimate aim of any nutrition program. The solution to iron deficiency anemia, or any other nutritional problem, depends upon an adequate intake of affordable, acceptable, nutritious foods. Foods must be available and the economic level of the population adequate to purchase them. Educational efforts must be broadly conceived, long-term in nature, and must involve the total educational, health, and agricultural organizations of the country. The solution depends upon an adequate food supply, either from domestic or foreign agriculture production, appropriately processed, distributed, and consumed by the population. Education concerning food and nutrition must be an integral part of any program.

VIII.
RECOMMENDATIONS

GENERAL

1. A permanent secretariat for INACG should be established to receive and distribute information on nutritional anemias and other subjects relevant to supplementation, fortification, and other programs for preventing deficiencies of hematopoietic substances. The secretariat should also schedule and prepare reports based on the discussions of INACG and its subcommittees. It should maintain liaison with other groups interested in nutritional anemias and with donor agencies. INACG should also develop and maintain a list of ongoing programs of anemia control.

2. Reference laboratories should be established to assist regional and country laboratories in developing and standardizing techniques, ensuring quality control, and training technical personnel.

3. A register of experts in different aspects of nutritional anemias should be compiled.

4. Task forces should be established to assist countries in the planning and development of programs to control nutritional anemias.

5. All intervention programs should include evaluation mechanisms.

6. Scientists and technicians from countries in which iron deficiency anemia is a major problem should be given additional biochemical and technological training in order to better develop programs within their own countries.

7. Effective educational materials should be developed and distributed to combat iron deficiency anemia.

ASSESSMENT OF IRON STATUS

8. Work should be continued to improve and standardize the methodology for measuring serum ferritin and the interpretation of the results in terms of iron status.

9. Research should be undertaken to develop simple field methods for the screening of subjects for anemia by semi-skilled personnel.

DELETERIOUS EFFECTS OF NUTRITIONAL ANEMIA

10. Additional studies should be conducted on the deleterious effects of nutritional anemias; in particular, investigations should be undertaken to explore the effect of iron deficiency on work output.

11. Work should also be continued on the specific effect of iron deficiency on muscle function, immune response, and behavior.

IRON FORTIFICATION

12. Further investigation of the technology of iron fortification of various vehicles, including the search for new vehicles and new iron compounds, is required.

13. Investigation of the relationship between iron absorption and the composition of the diet should be continued.

14. Further studies should be made to identify substances that promote or inhibit iron absorption, and to clarify their mechanisms of action.

15. The possibility of using enhancers of iron absorption in fortification programs should be further explored.

IRON SUPPLEMENTATION

16. Operational studies on the delivery systems for use in supplementation programs and the means of motivating target populations should be undertaken.

17. Additional work is needed to increase the acceptability of iron preparations and to reduce their side effects while maintaining adequate iron bioavailability.

18. A task force should be established to review the technology available for the development of slow release iron preparations.

19. INACG should develop a task force to review data and recommend action on parenteral iron preparations.

INTERVENTION STRATEGIES

20. Pregnant women generally should be given iron supplements. In a population with more severe iron deficiency, other target groups, such as school children, should also be considered for iron supplementation.

21. Fortification programs, as outlined in these guidelines, should be developed in any population where iron deficiency is significant. Supplementation programs may offer an interim solution and may very well be associated with accompanying fortification programs for some period of time.

INTERNATIONAL COOPERATION

22. Cooperation among research workers and supporting agencies should be encouraged.

a) Close international cooperation in solving the global problems of nutritional anemia is highly desirable because it facilitates the exchange of ideas and experience and stimulates all concerned. In addition, institutions experienced in developing and applying the more complicated laboratory methods should be encouraged to assist research groups with more limited resources and capability.

b) INACG should encourage close cooperation among supporting agencies by arranging meetings for the exchange of information and the identification of the more important areas for support.

Participants in the INACG meeting held 1-4 June, 1977, Göteborg, Sweden, at which time these guidelines were developed.

Attendees:

Dr. E. M. DeMaeyer (Chairman), World Health Organization, Geneva, Switzerland
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