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Iron Nutrition and the Fortification of Food With Iron

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At present, a high incidence of iron deficiency prevails in the infant and female population. Improvement in iron balance through fortification of food with additional iron is needed to prevent such deficiency. In the infant, this may be accomplished through the fortification of special food items whose use is confined to infancy. In the adult woman, an increase in fortification of flour and flour products to 40 mg/lb is proposed to accomplish this. Such manipulation of the public diet carries with it the responsibility of monitoring its effects on the iron balance of the population, and on the prevalence of iron deficiency and iron overload.

Iron deficiency is one of the most prevalent deficiency states affecting man. Its cause is a combination of the limited amount of iron which can be absorbed from the modern diet, and the occurrence of blood loss. The extent to which iron deficiency is nutritionally based, and the question of whether anything can or should be done about it is discussed.

Normal Iron Balance

"Essential" body iron amounts to about 35 mg/kg of body weight.[1] Since this is largely hemoglobin, iron deficits are generally recognized by a decrease in the hemoglobin concentration of the blood. An additional 0 to 20 mg/kg of iron may be present as ferritin and hemosiderin stores. While this iron is not essential, it serves the purpose of meeting acute requirements imposed by pregnancy or bleeding which exceed that available from the diet (1 to 3 mg/day). Body losses of iron are small, amounting to about 12μg/kg or 0.9 mg/day in the adult male, and about 20μg/kg or 1.3 mg/day in the adult female (excluding pregnancy).[2] In the normal individual, iron balance is regulated by changes in intestinal absorption, the "setting" of which is determined predominantly by body iron stores. Thus, the 70 kg (154 lb)-male in the United States, with his usual iron stores of about 1,000 mg, absorbs about 5.5% of a diet containing about 16 mg/day, while the average female, with iron stores of about 300 mg absorbs about 13% of a diet of 10 mg/day. The mean upper limit of food iron absorption found in the iron-deficient subject is about 20%[3]; in the individual with excessive iron stores the lower limit is not known. The relation between iron absorption and iron stores on the basis of mean data in normal men and women is shown in the Figure. In the normal individual, iron stores will increase as iron

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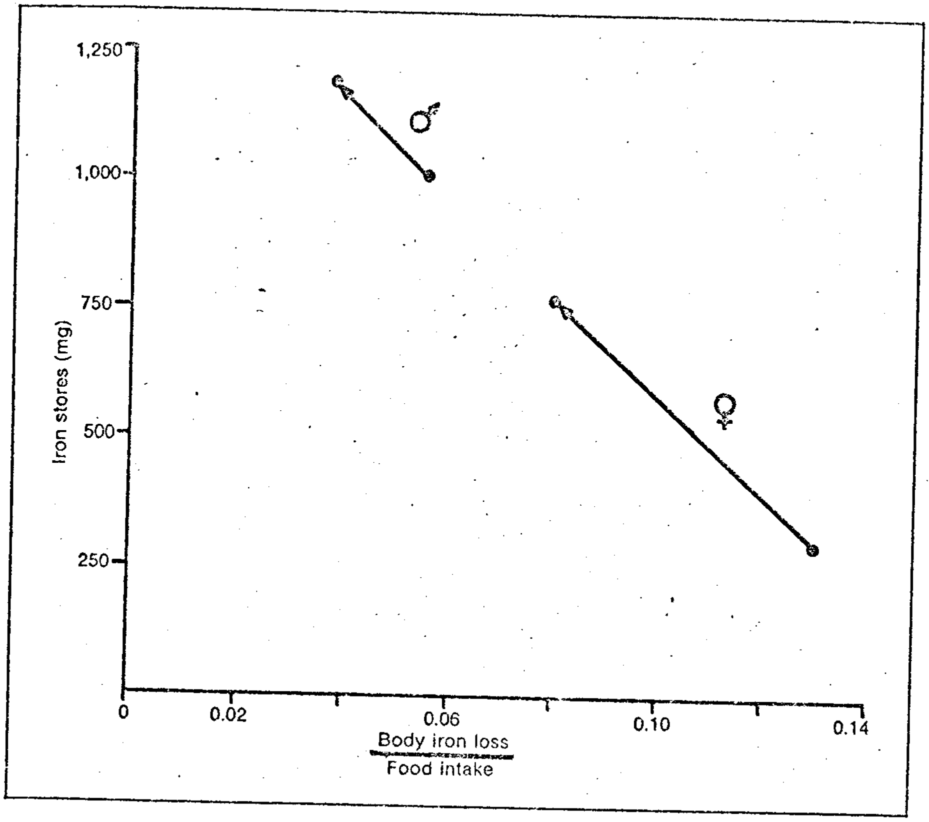

Fig 1.—Relationship between iron balance and iron stores. Iron balance is calculated from ratio of iron loss to iron intake; in normal male this is 0.9/16 or 0.056, and in normal female 1.3/10 or 0.13. Linear relationship is assumed between balance and stores. Anticipated change in stores due to increased fortification of flour (40 mg/day) is indicated by points at arrowhead.

intake increases, but the percent absorbed will decrease until a new equilibrium point is reached. Such a relationship is satisfactory as long as the intestinal mucosa regulates stores at a quantity of iron tolerated by body tissues.

Adequate iron balance has been defined as body iron content sufficient to meet physiologic needs. The adult male with normal absorption has no trouble with iron balance, unless some disease produces blood loss. In the adult female, an adequate iron balance is taken to mean the maintenance of sufficient storage iron to meet requirements of pregnancy, ie, iron stores in excess of 500 mg. In infancy, iron stores are virtually absent and would be difficult to create with iron taken orally. Adequacy of iron supply is best defined in terms of meeting the growth requirements of the expanding red cell mass.

The Problem

Iron balance is precarious in the infant, and in the female from adolescence to menopause. In infancy, both the cause and solution are clear. Iron stores become exhausted after the first few months due to a combination of very low iron intake and rapid growth. The incidence of iron deficiency in late infancy exceeds 25%.[4] Because of the low iron content of natural milk, iron depletion must occur unless the milk is fortified with iron, or unless other foods with appreciable iron content are given at an early date. An intake of 1 to 2 mg/kg per day is currently recommended[5]; this can only be reached by using milk fortified with iron, along with other iron-fortified foods. The problem in infancy is a special one in which the cause is largely nutritional and where food fortification with iron is entirely feasible. However, up to the present time fortification has not reached a large portion of the infant population.

In the adult male, the cause of iron deficiency is not nutritional. Some pathologic process is responsible, most frequently gastrointestinal bleeding. The demonstration of iron deficiency calls for an appropriate clinical investigation of its cause.

It is in the adult female that the problem arises.[4] Here iron balance is borderline, and anemia may result from normal events (menses, pregnancy, and blood donation). The term "nutritional deficiency" as applied to these women, does not necessarily reflect a poor diet in other respects, but rather that the average diet may be inadequate for the needs of a significant segment of the population. On this basis, some five million women in the United States probably have iron deficiency anemia, and perhaps five times that number are iron deficient in respect to iron stores. It appears that while the quality of the diet may have improved in the past few decades, the amount of iron ingested has decreased due to a decreased caloric intake and cleaner food. The results of iron depletion in the female population are several, leaving aside the debatable question of whether iron deficiency may produce symptoms through depletion of intracellular enzymes. Pregnancy is usually treated prophylactically with iron to avoid iron deficiency which would otherwise occur in over 25% of women; however, iron deficiency anemia continues in pregnancy because of delay by some pregnant women in contacting physicians, and because of the inconsistent intake of medication when prescribed. Regardless of whether the woman is pregnant or not, when iron deficiency anemia is identified, a difficult judgment must be made as to its cause: whether there is a nutritional basis, or whether a costly diagnostic workup for pathologic blood loss should be undertaken. When bleeding does occur in the iron-depleted individual, it results in an anemia of greater severity than would have occurred if stores had been present, necessitating, in some instances, transfusion with its hazards.

The question has been raised of the clinical significance of the usually mild anemia of iron deficiency, on the grounds that it produces little or no disability and no mortality. It does not seem appropriate to imply that a mild deficiency does not predispose to a severe deficiency, nor would it be consistent to treat the pregnant woman prophylactically with iron if it is of no consequence. The proper nutritional objective would seem to be the establishment of an optimal iron balance in the population at large. For these various reasons, the need for further fortification of food with iron to improve the female iron balance has been advocated. Such a decision rests on the feasibility of accomplishing this objective, and on its safety.

Food Iron Fortification

There is no question that iron added to food is absorbed, will improve iron balance and will reduce the incidence of iron deficiency anemia.[6] However, the benefit derived from added iron depends on the form of iron salts employed, the uniformity of intake of the food fortified, and the composition of the meal in which the food article is ingested. Current information concerning food fortification is clearly inadequate, but certain assumptions are reasonable. The best absorbed form of fortification iron is ferrous sulfate; however, other inorganic ferrous salts are probably also well absorbed. Such fortification iron has the same availability as other articles of nonheme food iron in the meal in which it is ingested. If the meal contains meat, total availability of nonheme iron may be as much as 20% in the iron-deficient subject; if meat is not contained in the meal, maximum availability drops to about 10%.[7] While heme iron is less influenced by dietary composition, and is well absorbed (about 20% in the iron-deficient individual), it represents only about 20% of dietary iron and usually less in the population with nutritional iron deficiency. At the present time the iron intake of the adult female amounts to 9 to 12 mg/day (6 mg/1,000 calories).[8] Twenty percent of this, or about 2 mg, currently comes from fortification of cereal, flour and flour products.

It may be estimated that the iron-deficient individual absorbs about 0.3 mg from this added iron. The level of fortification may soon be increased from between 13 and 16.5 mg/lb of flour to 35 to 40 mg, and fortification will be extended to all articles derived from flour (bread, biscuits, and rolls). If this is done, the average iron-deficient female may receive an additional 6 mg/day of iron, amounting to a maximal absorption of 0.9 mg from this source.[9] On the basis of existing knowledge of iron balance, this should result in a decrease in iron absorption from 13% to about 8%, and a mean increase in body stores from 300 mg to about 750 mg. This would be expected to decrease the frequency of iron deficiency anemia in the menstruating woman from about 5% to 1%, and should obviate the need for routine administration of iron in pregnancy. It is recognized that only mean values have been presented, and it will be important to determine the variation in intake of fortified food among the general population. It will be of further interest to determine the variation in composition of meals in which the food iron is ingested, since availability depends on this. Since mean estimates of the effects of augmented fortification are themselves only guesses, it seems pointless at this time to attempt to predict the variations in its effect on different individuals due to their different dietary habits.

Safety of Increased Food Iron Fortification

There is no question of the desirability of improving iron balance in the female if this can be done without hazard. Further fortification of food with iron, however, will increase the iron intake in the male, and the question of iron overload must be considered.[10] Parenchymal iron overload does produce dysfunction of the liver, pancreas, and heart, and may in some instances lead to death, as illustrated by patients with idiopathic hemochromatosis. The much greater incidence of this disorder in man (about 5:1) suggests that the manifestations of the disease are influenced by the more favorable iron balance in the male.

If the increased fortification of flour to 40 mg/lb is put into practice, it would be expected that the mean iron intake in the male would increase from 16.5 mg to about 25 mg.[9] A best guess is that this would lead to a decrease in iron absorption from 5.5% to 3.6%, and that iron stores would increase from 1,000 to about 1,300, but that equilibrium would be reached at this point. For the majority of the male population, this probably represents no increase over previous iron intake, since the iron content of food in recent years has decreased due to modern handling and cooking practices, and the total intake of food has decreased due to decreased physical activity.

The question of safety involves both the hypothetical danger to the normal man and a particular concern about individuals who have an inability to regulate iron absorption. In respect to the normal man, it is doubtful that amounts of iron in the range of 25 to 75 mg/day would have a deleterious effect. Studies of Ethiopians with an oral intake of 100 to 300 mg/day of iron as a dirt contaminant of food show no parenchymal iron overload, but this iron is of low availability.[11] Over several years intake of therapeutic amounts of iron has not been associated with parenchymal iron overload in the normal individual. The most impressive data concern the excess oral intake of iron in the Bantu, where parenchymal iron overload and tissue damage have been demonstrated.[12] This appears to be a unique situation in respect to both the amount of iron ingested and its availability. Some individuals consume 100 to 200 mg of iron per day in Kaffir beer over many years; the alcohol appears to enhance iron absorption, as does the lack of associated food intake. However, parenchymal iron overload from dietary iron in the normal individual would appear to be exceedingly difficult to achieve.

The problem of iron overload is not so much a matter of total body iron, as of an excessive parenchymal deposition of this iron (as compared to reticuloendothelial storage).[1] Parenchymal overload is seen in patients with genetic abnormalities in disposing of iron (idiopathic hemochromatosis), in patients with abnormalities of hemoglobin synthesis (sideroblastic anemia and thalassemia), in some patients with aplastic anemia supported by transfusions, and in some patients with chronic liver disease, especially on an alcoholic basis. In such individuals, it is reasonable to assume that any increase in dietary intake would increase parenchymal iron deposition and presumably result in an increase in the frequency and severity of clinical manifestations.

What then is the optimal iron balance for the general population, considering these opposite hazards? Iron depletion is clearly a high prevalence problem which can be met most efficiently by preventive measures. Iron overload, on the other hand, is a rare disorder which will occur regardless of manipulation of dietary iron intake, and whose therapy depends on iron removal through phlebotomy or chelate therapy rather than on decrease in intake. It would seem reasonable to approach the widespread problem of mild iron deficiency by nutritional means, but to deal with the relatively unique problem of iron overload by individual therapy.

Further Information Needed

Past attempts to improve iron balance have been carried out with limited knowledge of how to fortify food effectively, and with little appreciation of what was accomplished. It would seem irresponsible to institute the present recommended level of fortification without evaluating its effectiveness in respect to the type of iron employed, the extent to which it is consumed by the population at large, and its ultimate effect on body iron stores. It would also be desirable to carry out long-term studies using a diet fortified to approximately 50 mg/day to test the ability of the normal individual to maintain a suitable equilibrium at this level.

(Calculations of supplemental iron intake depend on (*a*) iron content of flour and derived products, and (*b*) the amount of these products consumed. At present, total iron content of fortified flour is 0.03 mg/gm. The proposed level of fortification (40 mg/lb) is 0.09 mg/gm. A baked product contains 60% flour. Flour products consumed are estimated to be about 150 gm/day, or 90 gm flour equivalent (estimates for adult females age 20 to 70 vary from 80 to 100 gm/day).[13,14] Current fortification involves only bread or a part of the flour equivalents consumed; future fortification is projected to include all baked items.)

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JAMA 75 YEARS AGO

March 13, 1897

Treatment of Hemophilia

The only advance in the therapy of this disease, has been made by Dr. E. A. Wright, who taking as a basis for his investigations the physiologic fact that a certain per cent of calcium salts is necessary for the coagulation of the blood, made a series of experiments with calcium chlorid, and demonstrated its efficacy in increasing the coagulability of the blood....

The following case that came under my care some time ago, will furnish additional proof of the value of this "physiologic styptic."

A. L., male; aged 20 years; nativity, Russia, came to my office April 2, 1895. He was suffering with an alveolar abscess, resulting from irritation produced by a carious tooth. A small incision one-eighth of an inch long was made through the mucous membrane, and a small quantity of pus evacuated. I was surprised that so small a wound should bleed so profusely, but thought that it would soon subside, consequently, a wash containing tannic acid was given and he was instructed to wait until the hemorrhage ceased. At this time I was called away from the office, and upon returning I was surprised when my assistant informed me that the bleeding still continued, and that the patient had lost a considerable quantity of blood. I then used a solution of perchlorid of iron and other styptics, but without success, and as pressure was of no avail, packing was tried, but it rapidly became soaked, and the blood showed no signs of coagulating. By this time the patient was on the verge of fainting. Finally after four hours energetic work, the hemorrhage was temporarily checked by packing the whole space between the aveolar process and the cheek with gauze saturated with a strong iron solution.

A careful inquiry into the patient's past history revealed the fact that he was one of a family of "bleeders." Expecting further trouble from the slight wound I had innocently made, the patient was sent to the hospital for observation. A few hours after his admission, Dr. Maisch, the interne, was called to see him for severe nose bleed, the epistaxis was profuse, and as the ordinary means failed to arrest it, it was necessary to plug the nares. Twelve hours later the hemorrhage from the wound recurred, the blood showed no signs of coagulating, and the bleeding only ceased when the patient was on the verge of collapse. The respite, however, was brief, and six hours later another alarming hemorrhage occurred, and after all the ordinary means had been used without success, Dr. Maisch suggested that we try the internal administration of chlorid of calcium. This was given in 1.30 gram doses, and in a few hours the effect was magical; the blood, which had showed no signs of clotting, began to coagulate, a firm clot formed, and the hemorrhage was completely arrested. The calcium salt was given in 1.30 gram doses every four hours during the first day, every six hours during the second day, and three times a day on the third, when its use was discontinued. The hemorrhage did not recur, and after the expiration of a few days the patient was discharged from the hospital, and passed from my observation.