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Symposium on

IRON METABOLISM AND ANEMIA

(Abstracts of Papers)

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Symposium on

IRON METABOLISM AND ANEMIA

(Abstracts of Papers)

Table of Contents

THE BIOCHEMISTRY OF IRON

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Because of its tendency to form complexes with many organic compounds, free ionic iron is not found to any significant extent in living organisms. The presence of iron in the molecule provides a positively charged atom of variable valency, which can form specifically directed covalent bonds with a number of organic groups or ligands. The complex, with iron at its "active center," may carry out one of several different functions: it may serve as an electron carrier, it may act to form a reversible combination with oxygen, or it may be instrumental in a catalytic attack. In the absence of organic components, the iron would not be able to perform these functions, or would do so less efficiently or in a less specific and controlled manner. Structure-function relationships are illustrated for hemoglobin.

In other biological iron complexes, such as serum transferrin, the iron may not play an active role. Transferrin protein packages and transports the iron in a nontoxic form. Because of its specific structure and ability to undergo conformational changes, the protein is also able to direct the entry of iron into those tissues that require it, and perhaps to play a regulatory role in iron absorption.

Hemoglobin and transferrin molecules contain four and two iron atoms, respectively. In hemoglobin, each iron atom is at the center of a protoporphyrin ring system and is also attached at one point to the protein. In transferrin, the protein provides six or seven iron ligands. Ferritin, the iron storage protein, is a different type of iron compound; its four thousand iron atoms, arranged in an "inorganic" colloidal complex, are covered by a protein shell which has channels that provide a means of entry or exit for the iron atoms.

The biosynthesis of both ferritin and hemoglobin is stimulated by the presence of iron. How this is achieved is a fascinating but incompletely answered question.

THE CONTROL OF IRON BALANCE BY THE INTESTINAL MUCOSA

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The small intestine controls the level of iron in the body, responding to the body's requirement and refusing to absorb available, unneeded dietary iron. The intestine receives information concerning the requirement and acts upon this information, absorbing more or less dietary iron as indicated.

It is suspected that a chain of phenomena controls these responses in approximately the following manner: (1) bleeding stimulates erythropoiesis, which increases the marrow's requirement for iron; (2) this accelerates the turnover of plasma iron, thus hastening the removal of iron from the intestinal mucosa and causing the concentration of iron in the mucosa to fall; (3) the intestinal epithelial cells formed in this iron-poor environment do not have the ability to refuse available dietary iron. When the intestine becomes covered with such cells the absorption of iron becomes increased. After the body's accumulation of iron is restored to normal, all these changes subside and the intestine once again can refuse to absorb available iron.

The injection of excessive iron has an opposite effect. The absorption of iron becomes less than normal. Some of the excess may be lost with the shedding of iron-laden phagocytes and epithelial cells.

THE ROLE OF PROTEIN IN IRON ABSORPTION

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Iron deficiency is common among populations consuming a protein-deficient diet and is detected with greatest frequency in women during the child-bearing years and in children during periods of maximal growth. Among protein-starved people, the factors that diminish iron absorption include (1) low dietary iron content, (2) little heme iron in the diet, (3) diminished corporeal stimulus to absorb iron, and (4) histological alterations of the small intestinal mucosa. In these same populations, a high birth rate, intestinal parasites, diarrhea, and chronic infection are frequent and contribute to the depletion of both protein and iron.

A protein-depleted diet is usually iron deficient as well, and most of the dietary iron is in an inorganic form that is easily chelated and rendered unsuitable for absorption. Many amino acids facilitate iron absorption by forming ligands with iron that keep it soluble at the alkaline pH of the duodenum; a low protein diet is deficient of these facilitating chelators. A dietary deficiency of substrates for body growth and hemoglobin synthesis decreases corporeal demands for iron and diminishes absorption of dietary iron. This can be demonstrated in acutely starved animals or in experimental animals maintained on starch, sucrose, or rice diets for prolonged intervals.

INTERSUBJECT AND INTRASUBJECT VARIATION OF IRON ABSORPTION

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The value of current isotopic methods for assessing iron assimilation in normal subjects is limited by the large range of absorption among different persons and in the same person on repeated testing. The contribution of methodologic errors to this variability was evaluated for measurements based on incorporated red cell radioactivity by comparing absorption from ^{55}Fe and ^{59}Fe administered simultaneously and at one-day intervals. In the simultaneous test, the differences observed were minimal. Administration of ^{55}Fe and ^{59}Fe on two successive days under otherwise identical conditions revealed two types of variability, roughly equal in magnitude. It may be concluded, therefore, that methodologic error or uneven distribution of the radioiron tag play an insignificant role. Intersubject variations reflect differences in the iron requirement of the individual and do not require overt iron deficiency for their expression. Intrasubject or day-to-day variations, on the other hand, represent an artifact of tracer methods, which result from differences in gastrointestinal secretion or motility at the time of dose administration.

The importance of these two factors from a methodologic standpoint depends on the type of absorption study being performed. When evaluating the form of administered iron, subject-to-stubject variation can be largely eliminated by expressing results in relation to absorption from a second dose of iron administered for reference purposes. This approach is particularly important in dietary studies, since it permits comparisons of foods in subject groups that differ in their overall iron needs. In comparing absorption from different forms of inorganic iron, intrasubject variation can be significantly reduced by administering multiple test doses over several days. When comparing absorption in different groups of subjects, variability must be compensated for by using a large enough number of subjects to attain statistical validity.

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For all these studies, it should be kept in mind that the abnormal frequency distribution of iron absorption values calls for modifications in conventional methods of statistical analysis in order to obtain meaningful results.

IRON ABSORPTION FROM FOOD

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Studies on iron absorption from food when iron is incorporated biologically have shown that it varies considerably according to the type of food and individual tested; it even varies within the same individual in consecutive days. Iron from vegetable food, especially from spinach, corn, and black beans, is poorly absorbed, with a mean of less than 2 per cent in normal subjects. The only exception is soybean iron, which shows a mean of absorption of from 16 to 20 per cent - comparable to the range observed for foods of animal origin. The rate of iron absorption from each individual food correlated significantly with inorganic iron absorption, and not with either plasma iron or percentage of transferrin saturation. The ratio of iron absorption versus inorganic iron absorption was less than 0.20 in the case of corn, black beans, and spinach; from 0.20 to 0.39 with wheat and lettuce; from 0.40 to 0.59 with fish, soybeans, and veal; and more than 0.60 with veal.

The administration in one meal of animal and vegetable food tagged with different isotopes showed that iron absorption from animal food is only slightly decreased or not decreased at all. On the other hand, corn or black bean iron was absorbed twice or three times better when mixed with animal food than when administered alone. Further studies have shown that amino acids, especially those belonging to the sulfur-containing amino acid group, enhance vegetable iron absorption in a manner similar to that observed with animal food.

These preliminary observations may help to explain why the prevalence of iron deficiency anemia in the absence of blood loss is less frequent in temperate zones than in tropical areas, since, even though iron intake in the latter is higher, more than 80 per cent of the dietary iron comes from vegetable sources.

BODY IRON TURNOVER AND EXCRETION

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Body iron may be labeled by injection of ^{55}Fe, the excretion of which can be measured by following red cell activity. In such studies one year must be allowed for equilibration with miscible body iron stores. Thereafter, the annual rate of iron loss from the red cell mass of normal adult male subjects is approximately 12 per cent, which is equivalent to a daily iron loss of 0.9 mg.

Iron loss from the gastrointestinal tract normally accounts for two thirds of the total amount and is derived from bleeding, exfoliation of gastrointestinal mucosal cells, and biliary secretion of iron. Other sources of loss include urine and skin exfoliation.

Information is more limited concerning variation in disease-related iron loss. With iron deficiency, the iron lost is reduced to perhaps one half the amount in a normal individual, whereas with iron overload it may be doubled. These losses, which are in the direction of normalizing body iron content, indicate the range over which balance may be achieved - as little as 0.5 mg/day in iron deficiency and as much as 2 mg/day with iron overload.

Iron balance in women is less predictable due to the variable iron losses associated with menstruation and pregnancy. The mean daily menstrual loss is 0.5 mg, but the range extends from virtually nothing to several milligrams. Likewise, the mean daily loss in pregnancy has been estimated as 2.5 mg, but it may be as much as 5 mg, and requirements are skewed as the last trimester approaches. In infancy, the status of iron balance depends to a large extent on the endowment of iron at birth, a function of birth weight. No good information is available concerning iron losses in infancy. However, precise definitions have been evolved regarding needs for growth and increase of blood volume; each kilogram increase in body weight brings with it an iron requirement of 25 mg.

HUMAN IRON REQUIREMENTS

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Nutritional requirements for iron are determined by the amount lost from the body, the amount needed to support growth and pregnancy, and the efficiency with which food iron is absorbed from the intestinal tract. In each instance, information is incomplete and variations among people are great. Statements about iron requirements must still, therefore, be regarded as intelligent estimates - not precise, but probably not far from the truth.

Data indicating that the iron lost by adults in urine, sweat, and feces varies from 0.5 - 1.2 mg/day can be regarded as a fairly accurate approximation; similar information about infants, children, and adolescents is very scanty. Mean menstrual iron loss averages an equivalent of about 0.5 mg/day; in 95 per cent of normal Scandinavian women the value was found to be less than 1.4 mg/day. The iron "cost" of a normal pregnancy includes the iron contributed to the fetus (200-370 mg), the amount in the placenta and cord (30-170 mg), and hemorrhage at delivery (90-310 mg); when one adds to these figures the normal external loss, the total varies from about 460 to 1130 mg, or from 1.6 to 4 mg/day. Lactation consumes roughly 0.5 to 1 mg/day, but is compensated for by the usual absence of menstruation during the period of lactation. The amount needed for growth is poorly defined but is determined by variations in the rate of growth during infancy and childhood and by the ultimate size attained; it is greatest during infancy and adolescence (0.5 to 1 mg/day).

Absorption of food iron is influenced by many variables: the kind of food (i.e., absorption is greater from meat than from cereals); the influence of foods on each other (i.e., cereals may decrease the absorption of iron from other foods); motility and the functional integrity of the bowel; presence or absence of normal gastric acidity; and the amount of storage iron present. Currently the best guess is that between 5 to 10 per cent of food iron is absorbed.

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On the basis of the data referred to and on an assumption of 10 per cent absorption, estimated dietary iron requirements for men and nonmenstruating women, menstruating women, pregnant women, adolescents, children, and infants are suggested.

IRON DEFICIENCY ANEMIA IN LATIN AMERICA AND CARIBBEAN POPULATIONS

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Iron deficiency anemias have long been identified as a major public health problem in parts of Latin America and the Caribbean, especially in population groups with high physiological iron requirements.

Reports from countries in this region show general hemoglobin averages ranging from 11 to 16g per 100 ml. A better analysis of the situation is obtained, however, when one considers the percentage of individuals classified as "low" or "deficient." In different countries the proportion of total population having less than 12g hemoglobin varies from 1.7 to 42.8 per cent for males and 3.6 to 49.1 per cent for females. The general average of MCHC was around 32 per cent, but the proportion of individuals in the general population who had less than 30 per cent MCHC varied from 1.5 to 18.0 per cent. Serum iron levels in general were low.

In some areas more than 30 per cent of the children under one year of age have a mean hemoglobin of 10g per 100 ml, and 50 per cent of the schoolchildren in some regions do not have a concentration even as high as this. Pregnant and lactating women are another group in which anemia constitutes an important public health problem in these areas. In Venezuela, for instance, 57.9 per cent of the pregnant women have less than 12g per 100 ml, whereas in the total female group only 18.9 per cent are below this level. Similar situations are found in other areas.

In random samples of pregnant women selected in Trinidad and Saltillo, Mexico, 34 and 50.9 per cent, respectively, had hemoglobin levels below 10g per 100 ml.

The PAHO Scientific Group on Research in Nutritional Anemias stated at a meeting in Caracas that in the towns of seven Latin American countries 21 per cent of the women in the last trimester of pregnancy are anemic.

A large proportion of the general population and of specific groups present blood parameters that are considered "deficient" or "low." If the population samples analyzed are representative of the general population of the area, it can be concluded that millions of people have unsatisfactory levels of hemoglobin concentration.

The rates of hemoglobin concentration, the proportion of low MCHC values, the generally low levels of serum iron, and the results of administration of iron to anemic populations in these areas strongly suggest that iron deficiency is the most general and important cause of anemia in Latin America and the Caribbean.

Malnutrition - resulting in poor absorption and poor utilization of iron - can constitute an important cause of iron deficiency anemia, and, indeed the diets of the people in this region are deficient and unbalanced, their principal sources of iron being of vegetable origin. However, studies of anemia, including dietary surveys or food analyses, suggest that in many cases dietary iron deficiency is only one of a number of factors that interfere in the deficiency of iron in the body.

Parasitic infection and anemia constitute frequently serious public health problems in the same populations. In a Brasilian survey in which 99.4 per cent of the results of fecal examination for helminths were positive, people with hookworm had a mean hemoglobin concentration constantly lower than those without hookworm infection. Antihelminthic therapeutic studies carried out in the Amazon basin in Peru showed a clear correlation between deparasitation and increase in hemoglobin concentration.

Further standardized studies using the same criterion in random population samples should be fostered. PAHO/WHO programs to standardize methods and techniques for obtaining more accurate data on the prevalence and etiology of anemias should also be encouraged.

Although many reports on iron deficiency anemia in these areas have been published, government-sponsored programs for the distribution of iron to the general population are not yet being carried out on a broad basis.

IRON DEFICIENCY IN PREGNANCY AND INFANCY

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Pregnancy and infancy are the most critical physiological stages for iron nutrition. During the third trimester of pregnancy the daily iron requirement is from 0.7 to 0.8 mg; during the first year of life the daily requirement is from 0.9 to 1.0 mg. Since no natural unsupplemented diet could be expected to provide iron in such large amounts, it would seem that these requirements should be met from individual iron stores or from supplementation. As a rule, however, adequate iron stores are uncommon in females of reproductive age, and, consequently, the prevalence of iron deficiency anemia in pregnant women is generally high, though its frequency varies from region to region, and even within a region, where it bears a relationship to the socioeconomic status and the eating habits of the population. Thus, definite anemia (hemoglobin below 10 gm/100 ml) has been observed in 40 to 50 per cent of the pregnant women in certain populations of India and Trinidad, but in only 0 and 2 per cent of Australian and Bantu women. In our studies of several groups of pregnant women living in poor socioeconomic conditions, anemia (hemoglobin below 12 gm) has been found in 19 to 36 per cent and iron deficiency (saturation index below 15 per cent) in 21 to 64.5 per cent.

Information is lacking on the subject of iron stores and the frequency of iron deficiency in infants, and in particular, on the influence, if any, of the mother's iron status on the amount of iron that the infant obtains from her. Observations have been confirmed, however, concerning the negative influence on the infant's iron nutrition of prematurity, low birth weight, early cord clamping, and fetal hemorrhage into the mother.

Hematological studies in full-term infants have shown that iron deficiency occurs with great frequency, and that this deficiency often starts between the 4th and 6th month, reaches its peak between the 10th and 18th month, and lasts for two to three years. In premature and low-weight infants the previously described pattern of deficiency is more marked, starts earlier, and lasts longer.

THE EFFECT OF HOOKWORM INFECTION ON IRON DEFICIENCY ANEMIA

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In hookworm-infected areas, some patients may be found with hookworm and no anemia and others with anemia and no hookworm. It has been repeatedly shown, however, that in areas of sufficiently intense infection, there is a rough statistical correlation between degree of infection, as witnessed by the number of ova in the stool, and circulating hemoglobin levels. In areas such as Venezuela and Brazil, where tests have been made, the circulating hemoglobin has been shown to rise slowly to normal levels after the hookworm load has been eliminated or markedly reduced, while the patients remain on their usual diet. This would seem to indicate that hookworm infection *may* be enough to cause iron deficiency anemia.

Other cases with such anemia in the absence of hookworm, or with light infection, may be explained by a past heavy infection, by reduced ingestion of iron (although this is rare in the tropics), or by reduced absorption. Many studies have now shown that the loss of blood induced by hookworm (*Necator americanus*) is of the order of 0.03 ml per worm per day, while *Ancylostoma duodenale* consumes from four to eight times as much. This would mean that an infection of only 250 *Necator* would lead to a daily blood loss of about 8 ml, implying an iron loss of 8 mg in the presence of normal circulating hemoglobin values. Part of this intestinal loss (about 30 per cent) is reabsorbed, but it is clear that hookworm infection can still contribute significantly to iron-deficiency anemia, although it may not be the only factor involved.

PREVENTION OF IRON DEFICIENCY ANEMIA

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In the past several years, nutritional iron deficiency among infants, schoolchildren, pregnant women, and nursing mothers has been well characterized. In spite of this information, little has been accomplished at the public health level to minimize the condition. Action programs must be initiated to correct the nutritional deficit.

In the prevention of iron deficiency anemia, several approaches may be considered. Long-term goals can be achieved through programs designed to improve dietary intake of iron by means of education and increased availability of iron-rich foods, and through environmental sanitation campaigns to control parasitism associated with blood loss. Immediate and short-term measures may consist of iron supplementation for vulnerable groups, such as schoolchildren and pregnant and lactating women, and enrichment and fortification of commonly consumed foods. The long-range and immediate programs can be conducted so as to supplement each other.

Assessment of the magnitude of the problem and location of individuals at risk throughout the country must precede consideration of ancillary benefits.

Iron enrichment of certain foodstuffs poses few if any technical problems; thus, the means to prevent the nutritional deficiency exist. Conflicting vested interests in agricultural production, commerce, and industry, however, have resulted in delays in the application of available remedies.

Prevention of iron deficiency anemia still remains a challenge to public health workers until such time as simpler and more effective techniques are developed to improve population iron stores and to meet the special requirements of vulnerable groups.