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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IRON DEFICIENCY IN WOMEN

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I.
Introduction

Although the amount of iron contained in even the most inadequate diet is considerably more than man's nutritional requirements, iron deficiency remains the most commonly recognized of the nutritional deficiencies. While it reaches its greatest prevalence and severity in developing countries, it is also frequently encountered in affluent societies. The explanation for this paradox lies in the poor bio-availability of much of the iron in present day diets. Our digestive systems are well adapted to the absorption of the heme iron in meat, poultry and fish,[97, 134, 151] it is the iron in rice, wheat, maize and other vegetable staples which is so poorly absorbed,[34] and much of the iron deficiency in the world can be ascribed to the virtual disappearance of meat from the diet of a large proportion of the world's population. The reason why man can absorb the heme in meat products so well and the non-heme iron in grain products so poorly is not known, but may relate, in part at least, to the fact that it is only comparatively recently in evolutionary terms that he has abandoned his hunter-gatherer lifestyle in favor of a more settled agricultural existence.[34]

The prevalence of iron deficiency in any population is a function of the bio-availability of the iron in the average diet, but varying requirements for iron largely determine which members of the population are affected. In this regard, infants and children are at special risk because of the increased requirements related to rapid growth.[92] In addition, women need more iron than men because of the superimposed requirements related to reproduction—menstruation, pregnancy and lactation. Both the prevalence and severity of iron deficiency are therefore considerably greater in women during their reproductive years than they are in men.

General guidelines for the eradication of iron deficiency were previously laid down by the International Nutritional Anemia Consultative Group (INACG) in 1977.[166] In a later publication, INACG concentrated on the special problems relating to iron deficiency in infancy and childhood.[92, 167] The purpose of the present monograph is to provide an update on the iron nutrition of women, with special reference to the requirements for pregnancy and lactation. To put these requirements into perspective, a brief summary of current concepts of external iron exchange will be given, since this information provides an essential background for any programs designed for the prevention or treatment of iron deficiency.

II.
Body Iron Compartments

Iron is essential for life. As a constituent of heme, it is present in hemoglobin, myoglobin and a variety of enzymes. In addition, there are a number of non heme iron enzymes. These various compounds subserve many vital functions; they are to be distinguished from storage iron, which is always present when there is sufficient iron within the body to permit the synthesis of the necessary quantities of the functional compounds. This reserve of iron is metabolically inert, being sequestered inside the molecules of a specialized, roughly spherical protein, ferritin. Ferritin iron is readily available when required for incorporation into functional compounds, such as iron-containing enzymes or hemoglobin. Most tissues normally contain only small amounts of stored iron, but the hepatocytes and the elements of the reticuloendothelial system in the various organs contain larger amounts, and serve as the main repository of the body's iron reserve. When the quantity of ferritin within a cell rises, some of it aggregates and eventually forms insoluble complexes which become visible by light microscopy, and stain blue with potassium ferrocyanide. These visible and insoluble aggregates of stored iron are known as hemosiderin.

The quantities of iron present in these several categories of iron compounds in a normal 55kg woman are shown in Table I. It is apparent that the largest amount by far is in hemoglobin, and the major metabolic iron circuit within the body is that involving the red cells. This circuit is largely a closed one, with much of the iron released from the hemoglobin of time-expired red cells being used again by the erythroid bone marrow for the production of new red cells.

TABLE I
IRON-CONTAINING COMPOUNDS IN A 55Kg WOMAN (approximate)

Functional Compounds	Hemoglobin	1700 mg
	Myoglobin	222 mg
	Heme enzymes	50 mg
	Non-Heme enzymes	55 mg
	Transferrin	3 mg
		2030 mg
Storage Complexes	Ferritin	200 mg
	Hemosiderin	70 mg
	TOTAL	2300 mg

The size of the body's iron stores is very variable, reflecting as it does the adequacy of iron balance over an extended period of time. In iron-replete men it reaches figures of about 1000mg in young adulthood, while in women consuming a good Western-type diet the figure is of the order of 300mg.[21] The lower figure in women is an indication of the more precarious balance between the amounts of iron which can be absorbed and their increased physiologic requirements. This point underlines the fact that when iron nutrition is less than optimal, it is the storage reserve that first becomes depleted. For this reason iron stores are often totally absent in adult women, especially in developing countries.[22]

III.
External Iron Exchange

Iron Losses

If adequate iron nutrition is to be maintained, the amounts absorbed from the diet must at least match the average daily losses from the body. In normal women these losses can be divided into the basal obligatory iron excretion and those extra losses incurred as a result of menstruation, pregnancy and lactation.

Basal Iron Losses Basal daily losses of iron from the body are derived from two major sources:—the desquamation of surface cells with their small amounts of functional and storage iron from the skin, gastrointestinal and urinary tracts, and the minimal gastrointestinal blood loss which occurs even in healthy individuals. There are also very low concentrations of extra-cellular iron in sweat, bile and urine. In normal men the daily loss is less than 0.1mg in the urine, 0.2-0.3mg from the skin and 0.6mg in feces.[1,2] Only about 0.14mg daily of the iron lost in the feces is derived from bile and desquamated epithelial cells; the hemoglobin content of erythrocytes makes intestinal blood loss much more significant for iron nutrition than is epithelial desquamation, and the remainder represents about 0.5ml blood. It is apparent that any increase in the amount of blood loss will have a profound effect on iron balance. In contrast, the skin does not represent an important source of iron loss and losses from this site are not increased in hot, humid environments where excessive sweating is a feature.[1,2] Total iron losses therefore amount to about 0.9-1.0mg daily (12-14 μg/kg/day). Because of the smaller body surface areas, the losses in women would be expected to be correspondingly less, and can be assumed to lie in the range of 0.7-0.8mg daily.

Menstruation Menstrual blood losses have been estimated in two large groups of women, the one Swedish[163] and the other British.[63] The Swedish women were randomly selected from the general population. In both studies the findings were strikingly similar, with median monthly losses of 30ml and 26.5ml respectively (Fig. 1). This is equivalent to 12-15mg iron, or expressed as a loss averaged over the whole month, 0.4-0.5mg daily. In both studies the distribution of menstrual blood loss was skewed to the right, with 10% of normal women having losses greater than 80ml. This is equivalent to more than 1mg daily and is thus greater than the combined losses from all other sources. Of practical interest in this regard was the observation that personal estimates of monthly blood losses can be very misleading[222] and 40% of the women in one study who were losing more than 80ml per period were unaware that their menstruation was excessive.[14] While there is a considerable individual variation in the amounts of iron lost via menstruation, there is surprisingly little variation from period to period in the same woman.[164] There is evidence that hereditary factors may be of importance in determining the menstrual blood loss.[234] Positive correlations with parity and with body size have also been shown. It is only when the amounts lost are very large (200ml or more) that endometrial abnormalities or fibroids are likely to be the cause.[234] Modern contraceptive practices can also significantly modify menstrual blood losses. For example, the mean menstrual blood loss is reduced to 12.7ml in subjects taking the combined variety of oral contraceptive,[63,164] but is increased to an average of over 50ml in those using intra-uterine devices.[63,176,228] (Fig. 2) Unfortunately the 'pill' is used more widely in

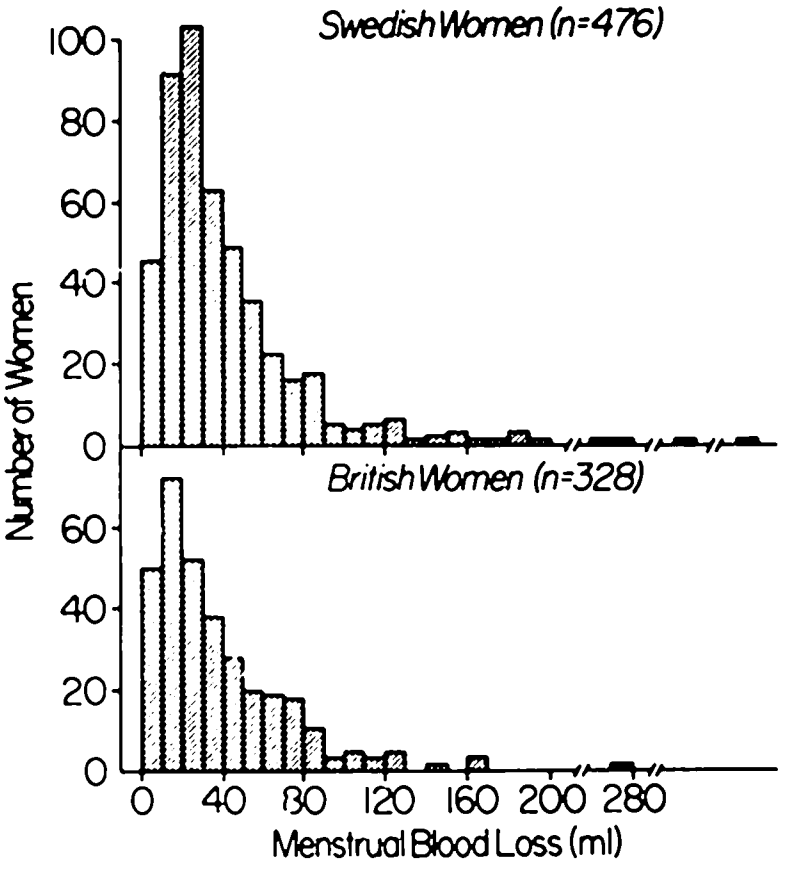

FIGURE 1

Frequency distribution of menstrual blood loss in two groups of women. The upper panel shows the results in 476 Swedish women (Data from Hallberg and coworkers[15]) and the lower panel those in 328 British women (Data from Cole and coworkers[62]) (After Goltner[138]). Reprinted with permission from *Iron Metabolism in Man*[137]

developed countries, where iron balance is much less precarious, than in those many developing countries where intra-uterine devices are more commonly employed. These various points are raised because they do suggest the need for obtaining data comparable to those already collected in Sweden and the United Kingdom in other population groups, and especially in those in which iron balance is most critically poised.

On the basis of his findings in normal Swedish women, Hallberg and co-workers constructed a graph indicating the expected iron requirements of this population (Fig. 3). In these calculations it was assumed that the average basal obligatory losses were 0.8mg daily (14 μg/kg in a 55kg woman).

From this graph it can be predicted that 50% of menstruating women would maintain adequate iron nutrition were they to absorb 1.4mg daily (0.8mg + 0.6mg), but in order for 90% of this population to remain in iron balance, the amount required would be 2.2mg daily (0.8 mg + 1.4 mg).

Pregnancy. While pregnancy is associated with a temporary cessation of menstruation, the overall cost to the mother in terms of iron balance is greater than in the non-pregnant state. Total iron

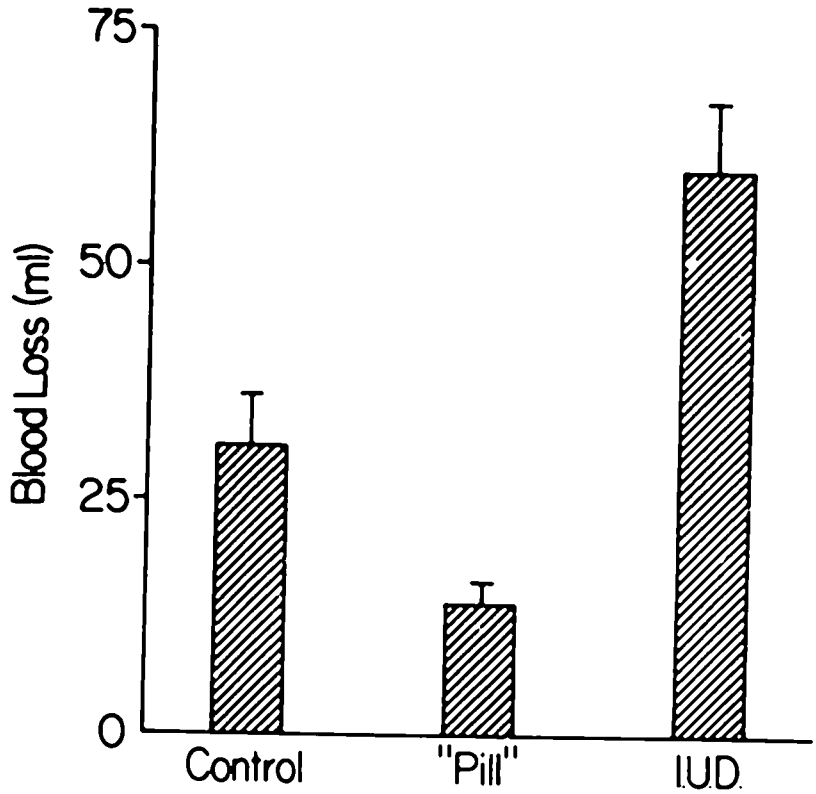

FIGURE 2

Mean menstrual blood loss (±SD) in 3 groups of women. The control group were normal women, the "pill" group were normal women taking the combined variety of oral contraceptives, and the I.U.D. group were women using intra-uterine devices. (Data from Hallberg and coworkers,[100] Nilsson and Solvell,[226] Cole and coworkers[63] and Gillebaud and coworkers[189]).

requirements of a 55kg woman amount to more than 1000mg,[317] but the net cost of pregnancy insofar as long term iron balance is concerned is a good deal less than this, since large part of the requirement is for the expansion of the maternal red cell mass, and most of this iron is returned to stores after delivery (Table II). If the demand for iron were evenly spread throughout the period of gestation, it could be met more easily by a rise in the absorption rate, but in fact the need for iron varies significantly in the three trimesters. During the first trimester iron requirements are actually reduced, since there are no menstrual blood losses and the amount of iron transferred to the fetus is minimal. From the beginning of the second trimester there is a major expansion in the maternal red cell mass which continues until well into the third trimester. When the iron supply is unrestricted this increase in the red cell mass eventually amounts to about 35%.[203,208,241,252] Expressed in terms of the need for iron these changes are equivalent to about an additional 450mg. The degree to which the need to expand the maternal red cell mass can be met is a function of the iron supply. In one study, for example, the mean increase in total hemoglobin iron was 570mg in a group of women given adequate iron supplementation as compared with 262mg in a group of normal women who were not given extra iron during pregnancy.[24] The fact that the red cell mass rises at a time when the oxygen requirements of the fetus are still modest suggests that the expansion results, at least in part, from a generalized increase in maternal oxygen consumption,[118] as occurs in hyperthyroidism. Despite the considerable

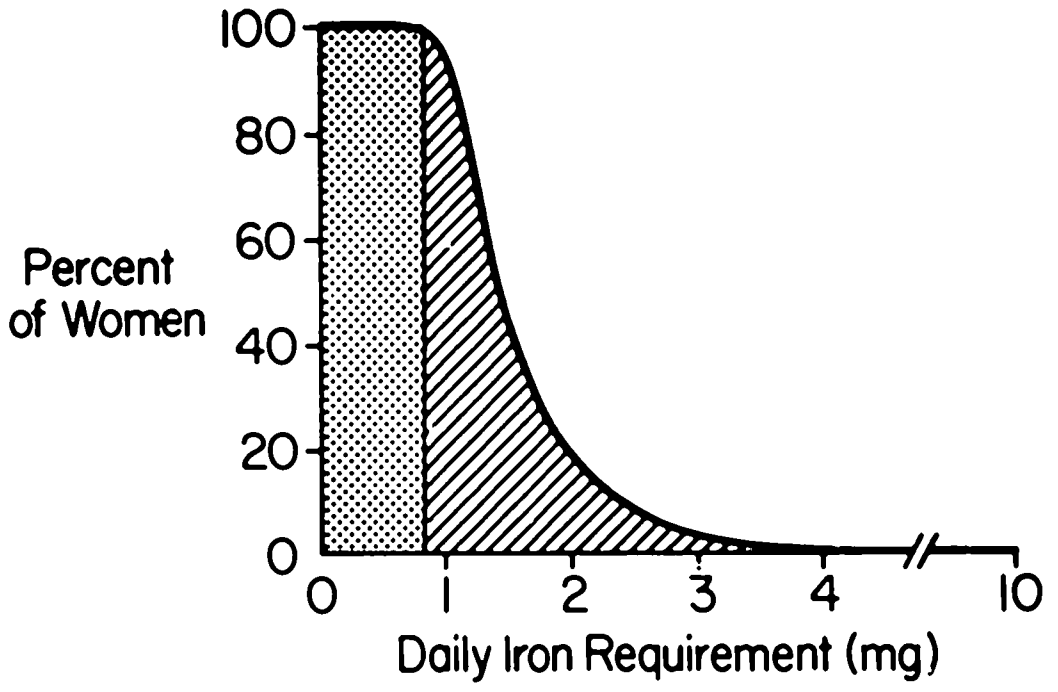

FIGURE 3

Cumulative frequency of daily iron requirements in normal women as calculated from the sum of their basal obligatory losses (dotted area) and that due to menstruation (cross-hatched area). (After Hallberg and coworkers[109]).

increase in the red cell mass that occurs in iron-replete women, the hemoglobin concentration tends to fall during the second trimester, the average drop being of the order of 1g/dl.[94] This "physiologic anemia" can be ascribed to the fact that the plasma volume increases to an even greater degree than does the red cell mass, with the result that there is a certain degree of hemodilution.

The requirements of the growing fetus, umbilical cord and placenta are particularly great in the latter half of pregnancy, since more than three-quarters of fetal growth occurs during this period. Expressed in quantitative terms the approximate iron requirements are shown in Table III. When these various requirements are seen in relation to those needed for the expansion in red cell mass (perhaps 300mg in the second trimester and 150mg in the third),[94] it is possible to calculate what average daily amounts are needed in each of the three trimesters if iron nutrition is to be optimal:

First trimester
± 1mg daily [Basal losses (0.8mg daily) + minimal fetal and red cell needs (± 30 – 40mg)]

Second trimester
± 5mg daily [Basal losses (0.8mg daily) + red cell needs (300mg) and conceptus needs (115mg)]

Third trimester
± 5mg daily [Basal losses (0.8mg daily) + red cell needs (150mg) and conceptus needs (223mg)]

An idealized diagram illustrating these needs is shown in Fig. 4. The daily amounts of iron required in the second and third trimesters are greater than can be met by absorption from the diet (see later section). However, if the mother enters pregnancy with a reasonable reserve of iron stored in the tissues, the first real demand of pregnancy, namely the increase in maternal red cell mass which begins

TABLE II
IRON LOSSES DURING PREGNANCY IN A 55Kg IRON-REPLETE WOMAN.
(These represent average values. Considerable individual variations have been reported in different studies).

	Amount of iron (mg)
Gross Losses	
Fetus	280
Umbilical cord and placenta	90
Maternal blood loss	150
Obligatory losses from gut, etc. during gestation	230
Expansion of material red cell mass	450
Gross Total	1200
Net Losses	
Contraction of maternal red cell mass after delivery	450
	750

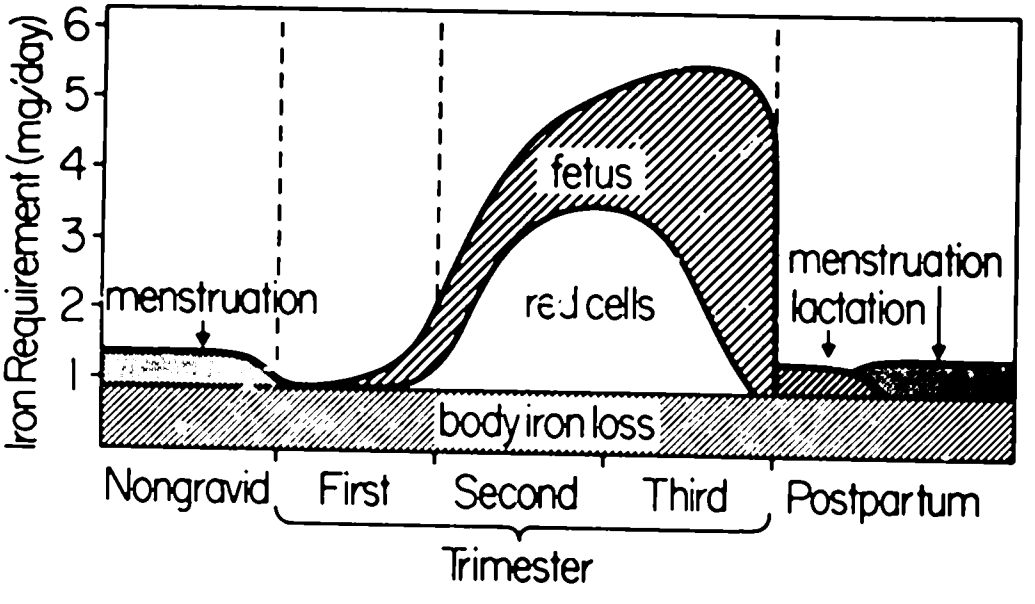

FIGURE 4

Daily iron requirements during pregnancy. These requirements are needed to meet the normal losses from the body and to provide iron for the enlarging red cell mass, the fetus and for lactation after the birth of the child (Redrawn with permission from *Iron Metabolism in Man*[31]).

at the end of the first trimester, can, in part at least, be satisfied. If the mother does not have a storage depot to draw on, and her diet is not supplemented with extra iron, she will become progressively depleted of iron during the pregnancy, since the needs of the fetus enjoy precedence over those of the mother. In this sense the fetus acts as a parasite, and there is now a good deal of evidence that the iron endowment of the infant is not normally affected by the iron nutrition of the mother.[illegible] At the same time, there is evidence that the delivery of iron to the fetus may be compromised, probably due to placental insufficiency, when there is severe maternal iron deficiency.[illegible]

To the iron requirements of the fetus and placenta, which can be regarded as true losses, must be added the iron lost as blood at delivery and as lochia later in the puerperium (vaginal discharge of blood following childbirth). While the total amount lost by these routes is usually about 150mg, there is considerable individual variation, and the loss can be further modified by a procedure such as episiotomy. The remainder of the iron used for expanding the red cell mass during pregnancy is returned to the stores after delivery and therefore does not figure in overall iron balance. The net cost of pregnancy over and above basal requirements is thus about 500mg (Table II). It should, however, be noted that these requirements are based on studies which have been done in Western countries. In most developing countries the body mass is about 20% less than the 55kg which has been taken as the average in these studies. The smaller body mass means that its iron content is less, and it seems reasonable to suppose that the additional iron needed for pregnancy is also proportionally lower. However, since the food intake, and hence the iron intake, is usually also reduced to about the same extent, the general conclusions concerning the need for additional iron remain applicable.

Lactation: Following delivery there is an interval of a number of weeks before menstruation recommences, but this potential saving insofar as iron balance is concerned is offset to some degree by lactation. The iron concentration of the breast milk is low,[illegible] falling from about 0.5mg/l during the first month after birth to about 0.3mg/l between 4 and 6 months of age.[illegible] The average daily maternal iron loss resulting from breast feeding is therefore also low, with estimated figures at 1, 2 and 3 months of 0.1mg, 0.28mg and 0.27mg, respectively.[illegible] While lactation thus does not normally represent a significant extra drain of iron, it can do so in those developing countries where breast feeding is continued long after the recommencement of menstruation. Expressed in terms of kilocalories, human milk contains less than 1mg iron/1000kcal, in contrast to the 6mg/1000kcal in the average mixed diet of developed countries.[illegible] However, the low iron content of breast milk is compensated for by the fact that it is highly bio-available to the infant.[illegible]

Pathologic Blood Losses: Basal losses in women can be affected by a number of pathologic conditions, the most important of which are those involving increased blood loss from the *gastrointestinal tract*. In this context, blood loss due to hookworm infestation is by far the most important, and its prevalence in some communities may be high enough for it to represent a significant epidemiologic factor affecting overall iron balance.[illegible] Daily blood losses are directly related to the worm load, being 0.02-0.10 ml per worm for *Necator americanus*, and approximately 2.4ml

TABLE III
IRON REQUIREMENTS OF CONCEPTUS BY TRIMESTER

	Fetus	*Umbilicus and Placenta*	*Total*
First trimester	25 mg	7 mg	32 mg
Second trimester	85 mg	30 mg	115 mg
Third trimester	170 mg	53 mg	223 mg
Total	280 mg	90 mg	370 mg

blood are lost per day when the infestation is sufficiently heavy to produce 1000 ovaig of feces.[109,110] Infestation with the other variety of hookworm, *Ancylostoma duodenale*, leads to proportionally greater daily blood losses (0.15-0.25ml per worm), but the parasite is less prevalent.[110] The deleterious effects of any given hookworm load on iron balance would be expected to be more prominent in adult women than in men because of their greater physiologic iron losses. At the same time it must be stressed that blood loss from the bowel is only one of the factors responsible for iron deficiency in areas where hookworm infestation is rife. The hookworm load is small in the vast majority of individuals in endemic areas, and other factors, such as a limited intake of absorbable iron, contribute to the widespread prevalence of anemia. In addition to hookworm, intestinal infestation with *Schistosoma mansoni* has been reported to produce significant fecal blood loss.[111]

Other causes of gastrointestinal bleeding have *clinical* rather than *epidemiologic* relevance. Gastrointestinal bleeding may arise in any site along the whole length of the gastrointestinal tract, and while bleeding hemorrhoids seldom escape the patient's notice, proximal sites may easily do so. As much as 1dl blood must be present in the stool to produce dark colored stools or melena,[112] whereas the continual loss of only a few ml each day will eventually deplete the iron reserve. Gastrointestinal bleeding may also be intermittent, and negative tests for occult blood in the stool do not rule out the possibility of a lesion. In one study of 378 patients, the bleeding was found to be due to hemorrhoids in 17% of the subjects, to salicylates in 13%, hiatus hernia in 12%, peptic ulceration in 12%, diverticulosis in 7%, neoplasm in 3%, ulcerative colitis in 3% and miscellaneous causes in 6%.[113] The site of the bleeding was not discovered in as many as 27%, and this group was followed for up to 21 years. Most of these subjects remained in good health, although in a number the bleeding continued. In some cases the cause of the bleeding was eventually elucidated, aspirin ingestion being the most common explanation.[113,114,115] Aspirin regularly increases the loss of blood from the gastrointestinal tract approximately fourfold to more than 2ml daily,[116,117] and large doses may increase it to more than 5ml daily.[117] Salicylates increase the exfoliation of the gastric mucosa and may produce erosive or hemorrhagic gastritis[118] in addition, they inhibit platelet aggregation and prolong the bleeding time. While aspirin is the most common offender, it is by no means the only drug which may cause gastrointestinal bleeding. Phenylbutazone, indomethacin and other non-steroidal anti-inflammatory agents have similar effects, and the corticosteroids may induce or aggravate peptic ulceration. Anticoagulant therapy will obviously enhance blood loss from any pre-existing lesion.

Pathologic losses also occur from the *genito-urinary* tract, the most common cause being uterine fibroids, which are present in about 40% of women losing more than 200ml monthly.[119] Bleeding from the urinary tract is rarely important for iron balance, since the presence of even small quantities of blood in the urine is immediately obvious and medical advice is sought. A rare cause of significant urinary iron loss is intravascular hemolysis: paroxysmal nocturnal hemoglobinuria may lead to a daily loss of as much as 10-15mg iron in the form of hemosiderin.[120]

Frequent *blood donation* soon produces iron deficiency in women unless adequate iron supplements are administered. In obscure cases of anemia the possibility of *self-induced bleeding* should be remembered.[121] The subject is usually a woman belonging to one of the paramedical professions, and thorough investigation has usually failed to establish the cause of the iron deficiency. Confirmation of the suspected diagnosis may be difficult or even impossible[15,22] without the use of whole body counting.[122] Another possible cause of iron deficiency is regular *hemodialysis*, the result of blood being left in the coil.[123,124] A rare cause is *idiopathic pulmonary siderosis*, a condition in which repeated bleeding into the lungs leads to the sequestration of iron there, so that eventually there is the paradox of pulmonary siderosis with iron deficiency elsewhere in the body.[22]

Absorption of Iron from the Diet

Three factors determine the amount of iron absorbed from the diet: the *behavior of the intestinal mucosa*, the *amount of iron ingested* and its *bioavailability*.

Mucosal Behavior. Not all the available iron within the lumen of the intestine is necessarily taken up by the mucosal cells. Their behavior is related to the iron content of the body, so that the percentage absorption rises as the body iron content falls.[25,40,74,125,126,127] In males, this homeostatic mechanism results in a decline in the rate of accumulation of body iron as adulthood is reached and the requirements for growth cease. The

average American man, with his body iron reserve of about 1000mg, only has to absorb daily about 6% of the 15-20mg iron in his diet to maintain a stable body iron content.[37] In contrast, the average American woman, who has an iron store of about 300mg, must absorb about 12% of the approximate 12mg iron in the smaller amount of food she consumes in order to meet her needs.[37,38] It is only when her iron requirements diminish to the male level after the menopause that the body iron reserve increases and the absorption rate falls. In the iron-deficient individual the intestinal mucosa is "set" to absorb large amounts of iron, but this only becomes apparent when soluble iron salts are administered, since the restricted bio-availability of much of the iron in the average United States diet prevents the attainment of high percentage absorptions. The uppermost limit of absorption of food iron by the iron-deficient individual on an average "good" diet appears to be about 4 to 5mg per day, but the figures are lower in most developing countries because the bio-availability of the non-heme iron is even less satisfactory.[219]

Iron Content: The iron contents of foodstuffs can be obtained from food tables, but some caution must be exercised in that if the iron contents of diets are measured, figures as much as double the listed amounts can be obtained.[143] Much of the extra iron is probably of extrinsic origin, either in the form of dirt or from the surface of the container or cooking utensil. The former is usually of very low bio-availability,[86,115] but iron derived from pans or skillets can add significant amounts to the absorbable iron intake, especially when the pH of the food being cooked in them is low.[222] In addition, cans may increase the iron content of preserved food by several mg.[25] These points are raised in order to underline the importance of direct analysis of foods if meaningful figures for iron intake are to be obtained. This is especially true in developing countries, where standards of food production and preparation vary widely. However, with the careful food handling that is now practiced in Western countries, there is usually good agreement between chemical analyses and estimates based on food tables.[25,223,224] Typical Western meals generally contain about 6mg iron per 1000kcal, with surprisingly little variation.[221,223] The iron is so well distributed among foods that little purpose is served by attempting to increase the iron intake by food selection.

Bio-Availability of Iron: It has become increasingly apparent in recent years that variation in the bio-availability of food iron is of far greater significance for iron nutrition than the iron content of the diet. The first point to grasp is the notable difference between the bio-availability of heme iron, which is easily absorbed whatever the dietary composition, and non-heme iron, which is usually of low bio-availability, being markedly affected by other ingredients in the meal.[210] Information on the relative bio-availability of iron in different foodstuffs was initially obtained using foods intrinsically labelled with radioiron. The striking difference that was noted was between the low bio-availability of iron in the three major grain staples-rice, maize and wheat (1 to 7% absorption)—and the much better absorption of fish and meat iron (12 to 20%) (Fig. 5).[100,215] The much better absorption of heme iron can be ascribed to the fact that heme is taken up into the mucosal cells as such, and the iron within it is therefore not vulnerable to the effects of gastrointestinal secretions and ligands derived from other ingredients in the diet.[46,100,244,250]

The importance of the heme content of the food is well illustrated by a study that was done of Swedish soldiers over a period of six weeks.[30] The average daily diet contained 17.4mg iron, 16.4mg of which was non-heme iron and 1mg heme iron. Only 5% of the non-heme was absorbed as compared with 30% of the heme iron. This meant that although the heme iron comprised only 6% of the total, it provided 30% of the amount absorbed. In another study the meal contained meat, black beans, maize and rice.[193] Its total iron content was 4.5mg, 1.5mg of which was in heme. In normal subjects the average total absorption was 0.46mg, 0.34mg being derived from heme and only 0.12mg from the non-heme fraction. The proportion of non-heme iron absorbed was, however, significantly greater in iron-deficient subjects, since it was 0.43mg of a total of 0.95mg. If these studies do nothing else, they underline the fact that heme iron, even when it forms only a small proportion of the total dietary iron content, is of great nutritional significance.

In contrast to heme iron, the bio-availability of the non-heme food iron is variable, but generally much lower. As was mentioned previously, this is particularly so in the case of the widely consumed staples, including rice, maize, wheat, black beans and soya beans.[100] However, such foodstuffs are rarely eaten alone; they usually form part of a mixed meal, and the proportion of the iron contained within them which is ultimately

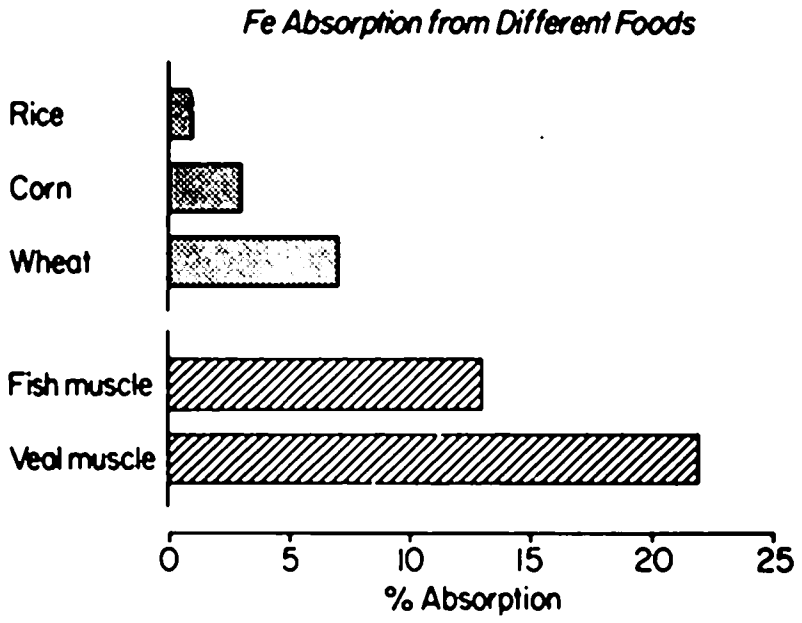

FIGURE 5

The geometric mean absorption of iron from grain products and from fish and meat by Venezuelan peasants. (Data from Martinez-Torres and Layrisse[111]).

absorbed is profoundly influenced by the composition of the meal. To understand why this should be so, it is necessary to have an understanding of the concept of the "common pool" of non-heme iron in the meal.[2,3,134] It has been shown that most forms of non-heme iron in a meal, whatever their origin, enter a common pool during the process of digestion, and are thus equally susceptible to the effects of a number of enhancers or inhibitors of iron absorption. This has made it possible to assess the total absorption of non-heme iron from mixed meals by simply adding a radio-iron tracer to the meal and measuring its absorption.

While a number of such studies have confirmed the validity of the "common pool" concept,[20,32,33,138,192,238,239,243] certain exceptions have been noted. The absorption of iron in the storage compounds ferritin and hemosiderin is significantly lower than that of vegetable iron. In addition, insoluble iron compounds, such as ferric pyrophosphate, ferric orthophosphate[23,138] and ferric hydroxide[88] are poorly absorbed, while ferric oxide is not aberbed at all. These observations have practical relevance, since such compounds in the form of dirt may contaminate foodstuffs such as cereals. It is therefore not surprising that there are occasional reports of the co-existence of nutritional iron deficiency in areas where the measured iron content of the diet has been found to be high.[4,221,243]

The role of the enhancers and inhibitors of non-heme iron absorption in a mixed diet is a complex one, since the amount ultimately absorbed is a function of a number of complex interactions.[120] Important in this regard are many different ligands of extrinsic origin in the form of other dietary constituents and the intrinsic secretions produced in the upper gastrointestinal tract. Conrad[63] has pointed out that the effects of any single ligand are determined by a number of variables. These include the concentration of the ligand, its affinity for both ferrous and ferric iron, the effectiveness of complexing in the changing physico-chemical conditions within the intestinal lumen, the nature and concentration of other ligands in the meal and, finally, the efficiency with which the complex can be absorbed by the mucosal cells. The major enhancers of non-heme iron absorption are ascorbic acid[29,43,96,100,230,239,240] and meat.[26,163,197,198] Ascorbic acid is not only a powerful reductant, but

also binds iron in equimolar concentrations to form a readily absorbed complex. Its promoting effect on iron absorption is dose-dependent (Fig. 6).[30,31,32,33]

The effect of ascorbic acid on non-heme iron absorption has been tested in a number of dietary settings, and in each case had been shown to be profound. It plays a particularly critical role in diets in which little or no meat is present. In considering the iron nutritive value of such diets it is therefore essential to have a knowledge of their ascorbic acid contents. Commonly consumed foods containing significant quantities of ascorbic acid are shown in Table IV. The effects of several of these fruits and vegetables on non-heme iron absorption have been directly measured and their promoting effect on non-heme iron absorption assessed. These include orange juice,[31,34] broccoli, cauliflower, potatoes and turnips.[39] On the other hand, the iron in spinach is poorly absorbed when fed alone (≈1–2%) despite its ascorbic acid content.[39,180] This suggests that it must be locked within an unabsorbable compound, or else that spinach also contains some powerful inhibitor(s) of iron absorption. The potential beneficial effects of ascorbic acid-containing vegetables was recently well demonstrated by Hallberg,[173] who compared two vegetable diets of similar iron content, which varied considerably in their ascorbic acid contents (Fig. 7). The large ascorbic acid content in the second diet was ascribable to the presence of cauliflower. While ascorbic acid is the dietary constituent in fruit and vegetables that has been most extensively studied in relation to enhancing non-heme iron absorption, it is almost certainly not the only one. For example, orange juice also

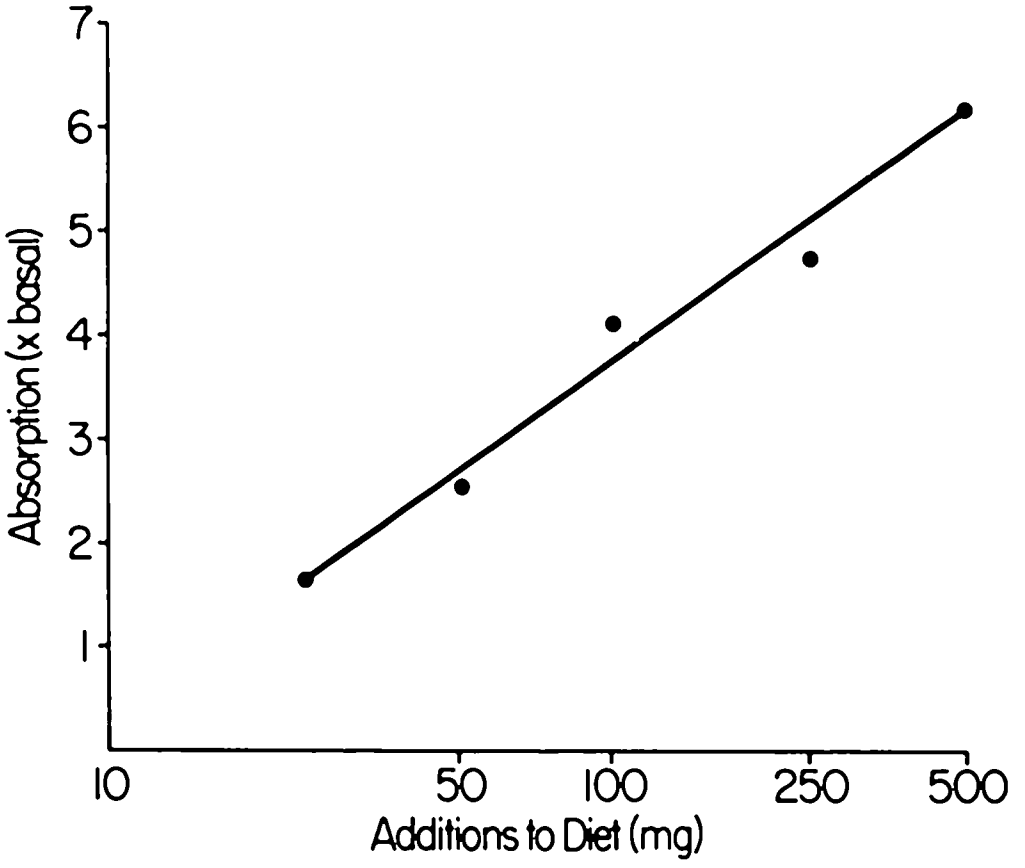

FIGURE 6

Effects of increasing quantities of ascorbic acid on the absorption of non-heme iron in food.

TABLE IV
APPROXIMATE ASCORBIC ACID CONTENTS OF A NUMBER OF FRUIT AND VEGETABLES
(Data from Documenta Geigy[101] and Paul and Southgate[224])

		Average Ascorbic Acid Content (mg/100g)
Fruit	Guavas - fresh	200
	- canned	180
	Lemons	80
	Oranges	50
	Pineapples	25
Vegetables	Broccoli - boiled	34
	Cabbage - raw	60
	- boiled	15
	Cauliflower - raw	60
	- boiled	20
	Peas - raw	25
	- boiled	15
	Potatoes - new boiled	18
	Sweet Potatoes - raw	25
	- boiled	15
	Spinach - boiled	25
	Tomatoes - raw	20
	Turnips - raw	25
	- boiled	17

contains citric acid, while sauerkraut, which is a potent enhancer of iron absorption,[133] contains lactic acid, a known enhancer of iron absorption,[93] in addition to ascorbic acid, and also has a low pH; the solubility of ferric ions in particular is pH-dependent.

In an earlier section it was mentioned that the heme iron in meat, poultry and fish is well absorbed, but meat fulfills another important role in iron nutrition; it potentiates the absorption of non-heme iron in other foodstuffs (Fig. 8). How this effect is mediated is not known, but it may relate to the release during digestion of amino acids and polypeptides in the upper small bowel, and the formation of soluble, absorbable complexes with the non-heme iron.[76,143,192,194]

A number of inhibitors of iron absorption have been recognized in the past. These include carbonates, oxalates, phosphates and phytates.[65,123,149,244] Many diets contain large quantities of one or more of these substances and it has been suggested, on the basis of *in vitro* studies, that they form large complexes with iron which are very poorly absorbed. However, the degree to which such complexes inhibit iron absorption is variable. Monoferric phytate, for example, which is the main form of iron in wheat, is as available for absorption in a mixed meal as is ferrous sulfate,[206] while dephytinized wheat bran still has the capacity to inhibit non-heme iron absorption.[223] Furthermore, beetroot has a very high content of oxalic acid, which has been claimed to inhibit iron absorption, and yet non-heme iron is well absorbed when fed with beetroot.[19,133] At the same time there is firm evidence that certain dietary components do have a profound inhibiting effect on iron absorption. The absorption of iron in bread drops progressively as its bran content rises (Fig. 9).[29] In another recent study a negative correlation was found between iron absorption and fecal bulk, and it was suggested that some factor or factors in vegetable fiber may have an inhibiting effect on non-heme iron absorption.[232] When Indian tea is fed with a variety of meals there is a marked reduction in iron absorption, which has been shown to be due to the formation of insoluble iron

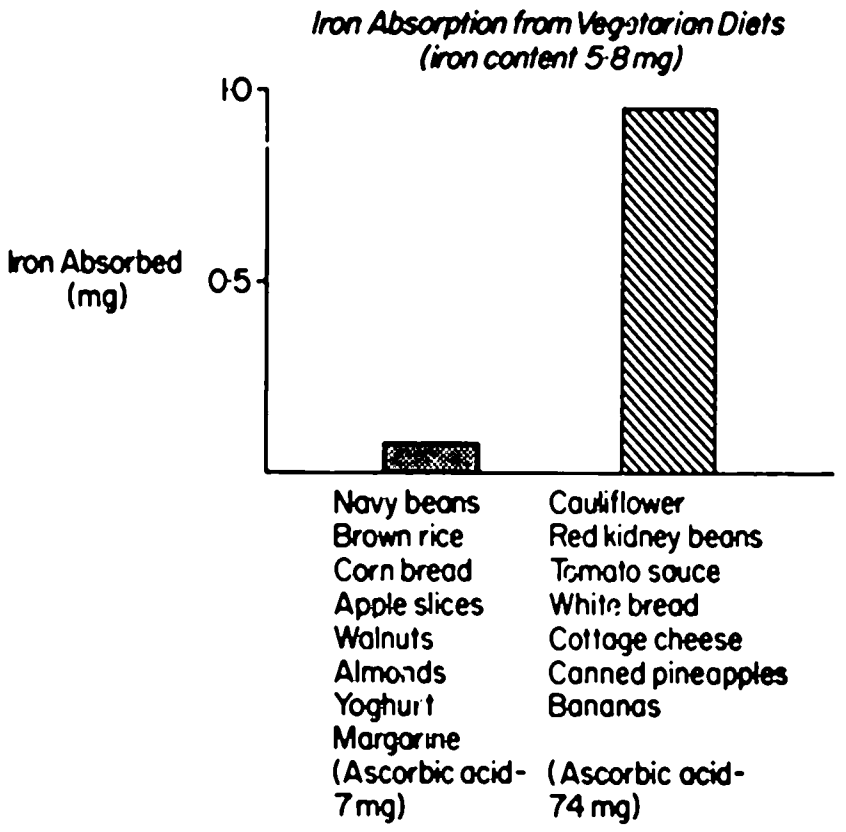

FIGURE 7

A comparison of the absorption of non-heme iron from two vegetable meals containing differing quantities of ascorbic acid. The difference was largely ascribable to the presence of cauliflower in the one meal. (Figure from Hallberg [132] Redrawn with permission)

tannates (Fig. 10).[100,101] This observation may well have relevance to iron nutrition, since tea is drunk with meals in many parts of the world. Another inhibitor of non-heme iron absorption that has been well studied is egg yolk. It contains a phosphoprotein which binds iron strongly.[131] Other inhibitors may have relevance in certain situations. For example, ethylenediamine tetra-acetic acid (EDTA), which is used as a food preservative, causes a 50% reduction in the absorption of non-heme iron from a typical American dinner when the EDTA to iron molar ratio is 2:1.[32] There is evidence that such ratios do, in fact, occur in the United States diet since EDTA is present in some foodstuffs and drinks, including margarine and both carbonated and malted beverages. The degree to which enhancing and inhibiting agents affect iron absorption from a standard meal was well demonstrated in a recent study in which a standard continental breakfast was fed together with different beverages, two containing inhibitory substances and one an enhancing one (Fig. 11). A threefold difference in the amounts of iron absorbed was found. When a promoting agent and an inhibiting one are both present in the same meal, the effects are antagonistic. Orange juice increases the absorption of the iron in porridge or bread[33,132] and in eggs[131] while if an egg is fed together with bread, the poor absorption of the bread is further reduced.[33,106,107]

Endogenous Ligands: During peptic digestion a proportion of the non-heme iron in food is rendered ionizable,[169] while heme is released from its

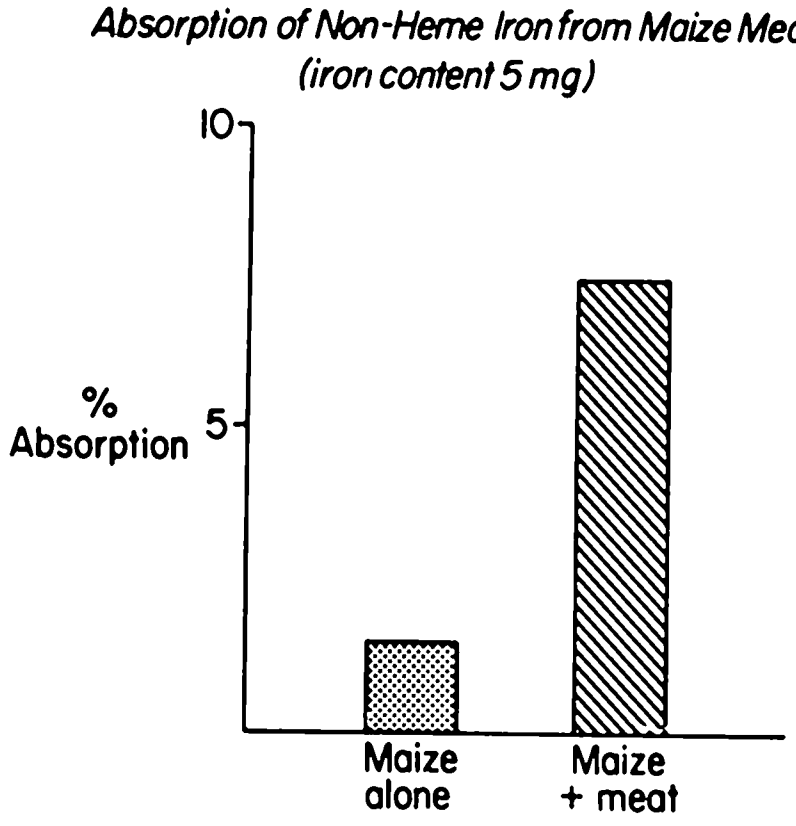

FIGURE 8

Absorption of non-heme iron from a maize meal in the absence and presence of meat. (Data from Layrisse and coworkers[189]).

globin bonds.[46] Gastric hydrochloric acid plays a key role in this regard, and there are several studies showing its importance in the absorption of ferric iron salts[49,125,171,241] and of non-heme food iron.[27] Its importance presumably relates to the fact that polymeric iron complexes are less likely to form at low pH. While other gastric juices must obviously have relevance to iron absorption in that they promote digestion with release of iron from the food, there is little evidence that they contain any component that acts as a specific carrier for iron.[27] There is also no evidence that pancreatic, biliary and intestinal secretions have a direct effect on iron absorption.[27] At the same time it seems possible that the proteolytic pancreatic enzymes may have an enhancing effect on iron absorption in certain dietary settings, since they release amino acids or polypeptides which can act as promoting ligands for iron absorption. Such an effect is, however, unlikely to be a major one, since iron absorption is not reduced in patients with chronic pancreatitis.[14,92,151,177]

Overall Effects of Ligands on Non-Heme Iron Absorption: From the preceding discussion it is clear that there are may ligands that can influence the absorption of iron from a particular diet. Considerable attention has been paid to the possible inhibitory ligands present in cereals, since they seem to contribute so much to the nutritional iron deficiency that affects many population groups. While there is no doubt that substances such as bran and tannates can profoundly inhibit iron absorption, the inadequate amounts of enhancing ligands in cereals may be of equal or even greater significance. Support for this contention has been

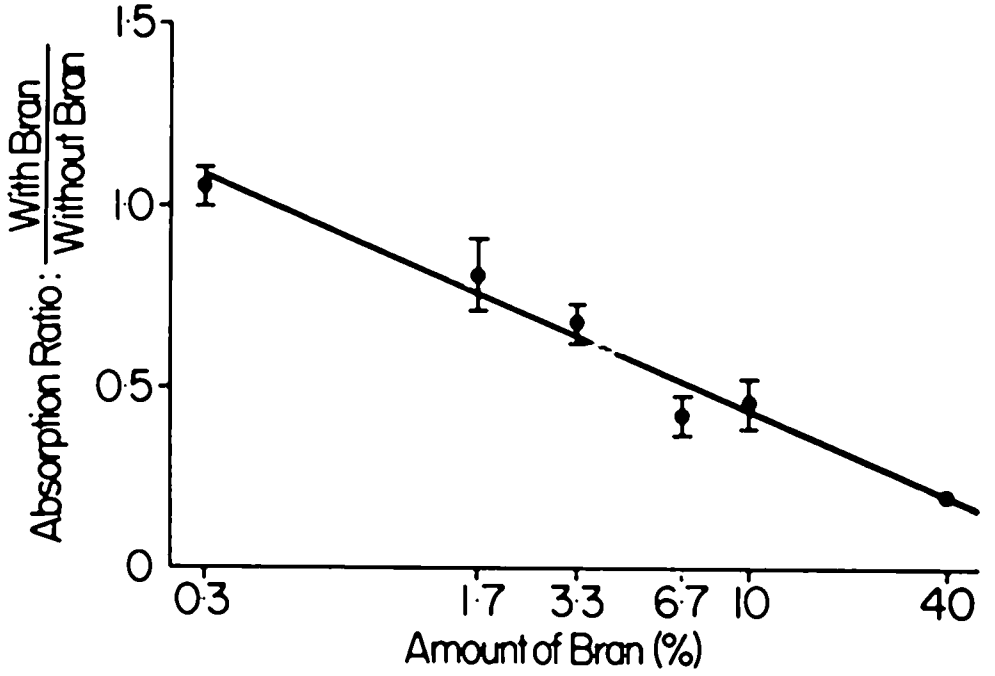

FIGURE 9

The inhibitory effect of an increasing percentage of bran on the absorption of iron from wheat bread. (After Björn-Rasmussen.[18] Redrawn with permission).

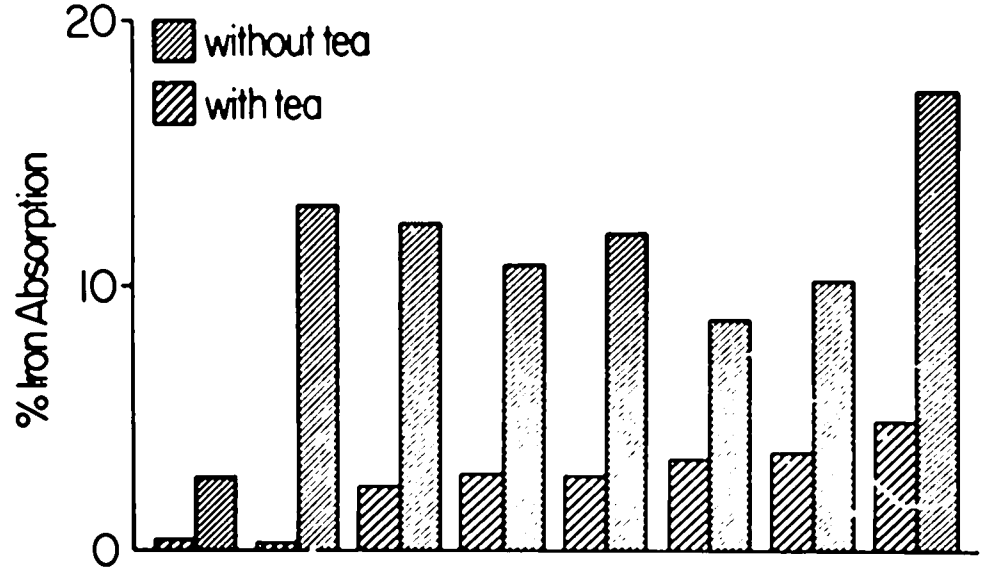

FIGURE 10

The inhibitory effect of tea on the absorption of the non-heme iron in a meal containing rice, potato and onion soup, and 100 mg ascorbic acid (Data from Disler and coworkers[19])

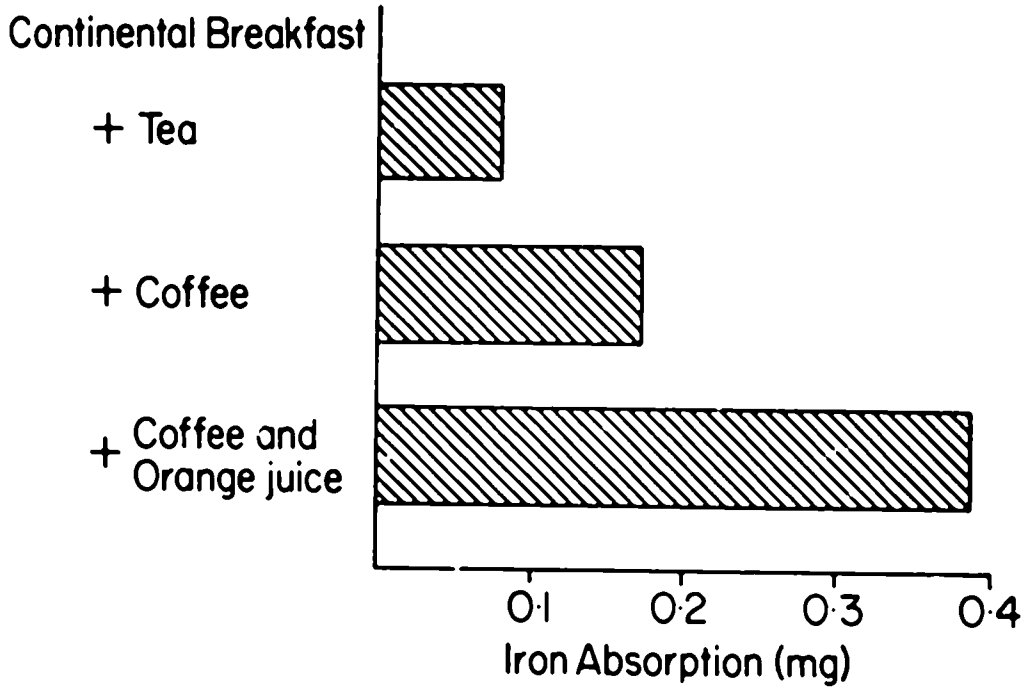

FIGURE 11

Effects of different beverages on the absorption of iron from a continental breakfast. (Data from Rossander and coworkers[231]).

obtained in several studies in which it has been shown that iron absorption from rice, maize and wheat meals is markedly increased when ascorbic acid is present,[78,99,230,232,234] and similar improvement in non-heme iron absorption has been noted when meat has been added to a maize porridge meal.[175] On the basis of these various studies it is now possible to predict with a degree of confidence how much non-heme iron will be absorbed from different diets, depending on the relative contents of the two major promoting agents, ascorbic acid and meat, poultry or fish (Fig 12). A diet of low iron bio-availability is one in which the daily ascorbic acid content is less than 25mg or the meat, poultry or fish content is less than 30g, while one of high bio-availability is one with more than 75mg ascorbic acid and or more than 90g meat, poultry or fish. Anticipated percentage absorptions from these different meals by subjects with no iron stores would be 5% and 20% respectively.[219]

If these figures are seen in relation to the iron requirements of females, it is possible to make certain generalizations concerning the quantities of iron which must be present in different diets if iron balance is to be maintained. In calculating iron requirements allowance must be made for the wide variation in menstrual losses among normal women. Since median menstrual losses are equivalent to 0.4-0.5mg iron day, with the basal losses of 0.8mg day, half the female population would remain in iron balance if 1.3mg could be absorbed daily. For this to be true of 80% of the women, the figure would need to 1.8mg and for 95% of the women, 2.8mg. The amounts of iron that would need to be present to meet these needs in diets of differing bio-availability are shown in Table V. Unfortunately it is not easy to translate the message of the figures in Table V into practical intervention strategies, since it is clear that economic factors are largely responsible for the inability of so many people in the world to maintain adequate iron nu-

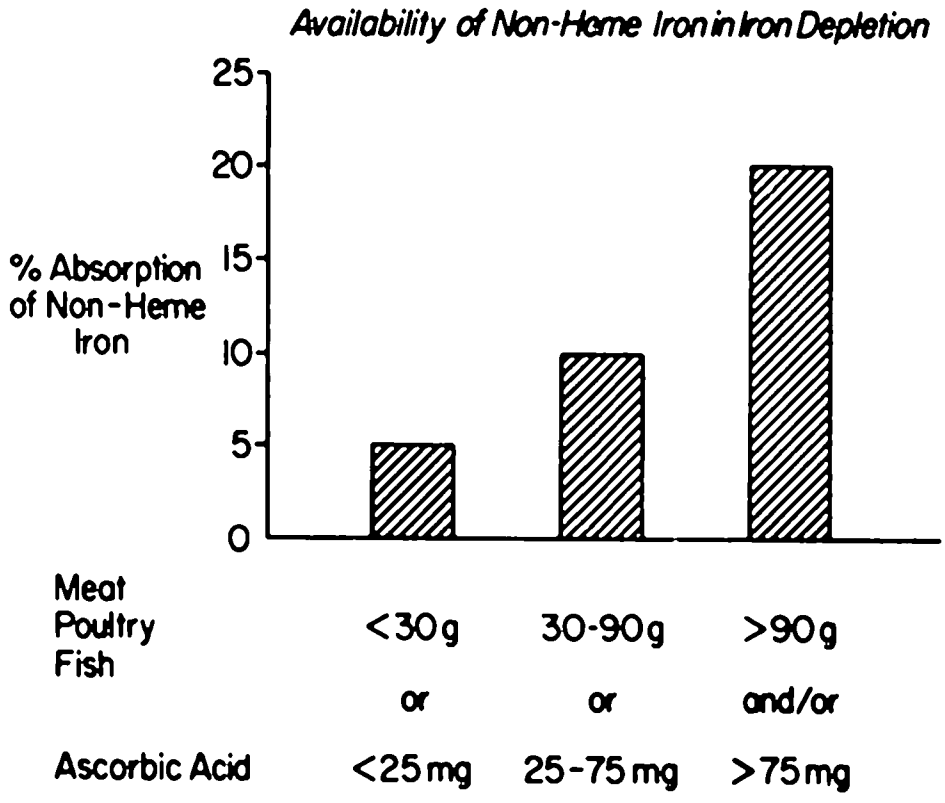

FIGURE 12

The percentage absorption of non-heme iron by individuals with no body iron stores from 3 different types of diet. A daily diet of *low availability* is one containing less than 30g of meat, poultry or fish (lean, raw weight) *or* less than 25mg ascorbic acid. The comparable figures for a diet of *medium availability* are 30 to 90g meat, poultry or fish *or* 25 to 75 mg ascorbic acid, while a diet of *high availability* is one containing more than 90g meat, poultry or fish *or* more than 75mg ascorbic acid. Alternatively it is one containing 30 to 90g meat, poultry or fish *plus* 25 to 75mg ascorbic acid. (Data from Monsen and coworkers[119]).

TABLE V
DAILY AMOUNTS OF IRON REQUIRED IN DIFFERENT DIETS

	Iron in Diet (mg)		
Daily Iron Losses	*Low Bio-availability*	*Medium Bio-availability*	*High Bio-availability*
1.3 mg (50% of women)	26	13	6.5
1.8 mg (80% of women)	36	18	9
2.8 mg (95% of women)	56	28	14

trition: meat is beyond the means of vast segments of the earth's population, and even the fresh fruits and vegetables which contain adequate amounts of ascorbic acid are more expensive than rice, wheat maize and other staples, the iron of which is so poorly available unless absorption-enhancing ingredients are present. In developed countries the problem is of a different nature, with excessive food refinement and decreased caloric intake having special relevance. The quantity of food eaten per day has declined significantly in the recent past because the amount of energy needed for daily living has diminished.[14,232] The sedentary lifestyle of many people has reduced the energy requirement and, as a direct consequence, the iron intake has declined.

Pathologic Malabsorption of Iron: The predictions in Table V will obviously be inaccurate if gastrointestinal pathology interferes with the absorption of iron. In countries such as India, Haiti, West Pakistan and Bangladesh, malabsorption associated with bowel disease is common.[17,29,194,199,231] However, malabsorption is a much rarer cause of iron deficiency than is pathologic bleeding. Iron absorption is defective in idiopathic steatorrhea[231,233] and may indeed be the presenting feature, although absorption of other nutrients is usually also defective. Among these is folate, so that the red cells are frequently dimorphic, and the mean corpuscular volume (MCV) may not be within the iron deficiency range. Gastric surgery may lead to inadequate iron absorption, probably due both to the loss of the normal "hopper" function of the stomach and to the diminished gastric secretions.[124] Vagotomy[175] or vagotomy plus drainage of the stomach[87] have less effect on iron balance than Billroth II (excision of the stomach) and Polya (gastrojejunostomy) operations. It has been shown that the absorption of both non-heme[276,299] and heme iron[146,213,276] in food is defective after gastrectomy, and in women under 50 the hemoglobin concentration has been found to fall at a rate of about 0.9g/dl per annum. In postmenopausal women the rate is only 0.3g/dl.[9] Bleeding may contribute to the iron deficiency in such subjects.

Since gastric hydrochloric acid promotes the absorption of non-heme iron,[27,49,125,171,212] it is not surprising that an association has been noted between chronic gastritis and iron deficiency. This is, however, not due only to malabsorption of non-heme iron, since intermittent bleeding from the atrophic mucosa may also be a contributory factor. In addition, there is evidence that the reverse may be true, namely that iron deficiency may cause gastric mucosal atrophy: repair of the iron deficiency may lead to some improvement in the mucosa, particularly in younger patients.[133] Pica, or the eating of non-food material, may lead to iron deficiency depending on the substance consumed. The range is wide, including earth, clay, pebbles, laundry starch, ice, wall plaster and charcoal.[112] Pica has been recognized in many parts of the world, including the United States,[49,83] Iran,[241] Turkey,[231] South America,[142] India,[145] and Africa,[232] and while it has been observed in both sexes, it is more prevalent among pregnant women, particularly when the socio-economic circumstances are poor. Not all the substances consumed affect iron absorption, but certain clays have been shown to adsorb non-heme food iron and render it unavailable for absorption.[231] Medicinal antacids have a similar effect. Tetracyclines form insoluble complexes with iron and would be expected to interfere with iron absorption, but long-term tetracycline therapy for acne has not been shown to produce detectable disturbances of iron balance.[133]

IV.
Deleterious Effects of Iron Deficiency

Any intervention program aimed at reducing the prevalence of iron deficiency in a particular population is predicated on the assumption that nutritional iron deficiency does indeed lead to significant disability. It is therefore important to review briefly the evidence that this is so.

The most obvious end result of iron deficiency is anemia, and it is therefore not surprising that this has been taken as the major yardstick in measuring the possible ill-effects of iron deficiency. There is, however, recent evidence that adverse effects may also result from the iron deficiency of other tissues in the body, and this evidence will be reviewed.

Effects of Depletion of Hemoglobin: The best clinical evidence on the deleterious effects of severe nutritional anemia has been noted in pregnant Malayan women, the maternal mortality was reported to be 15.5/1000 among those with hemoglobin concentrations less than 6.5g/dl as compared with a figure of 3.5/1000 in a non-anemic group.[illegible] Prenatal and perinatal infant loss and the rate of prematurity were also all significantly higher, but since folate deficiency was a complicating feature in a number of the anemic subjects, the exact role of iron deficiency remains uncertain.

Several physiologic studies have shown that iron deficiency anemia can affect effort tolerance, with a reduction in maximum work capacity. Several studies in rats and in man[illegible] have shown a significant correlation between the hemoglobin concentration and work capacity, with the results of some studies indicating that even minor decrements affect performance (Fig. 13).[illegible] These latter findings are somewhat surprising, since there are several compensatory mechanisms that safeguard the delivery of oxygen to the tissues, including adjustments in cardiac output and in the affinity of hemoglobin for oxygen.[illegible] In this regard, it should be noted that there are, in fact, studies in rats[illegible] and man[illegible] in which significant changes in physical performance were noted only when the hemoglobin concentration fell below 10g/dl.

The translation of these physiologic findings into clinical terms is not easy because of the many variables involved, but there are at least two studies in which evidence has been obtained suggesting that manual laborers suffering from iron deficiency anemia are less efficient workers than are subjects with normal hemoglobin concentrations.[illegible] The evidence was obtained in male workers on a rubber plantation in Indonesia[illegible] and in female workers on a tea plantation in Sri Lanka (Fig. 14).[illegible] In both studies the performance of the iron-deficient subjects improved when iron therapy was given, the greatest improvement being in those with the lowest initial hemoglobin concentrations. However, it is not clear whether this improvement was due to the repletion of hemoglobin only or whether correction of a deficiency affecting some other iron-dependent metabolic process was also a factor (see later section).

Depletion of Other Iron-Containing Compounds: A number of iron-containing and iron-dependent compounds are depleted in iron deficiency anemia (Table VI).[illegible] When depletion of one or more of these compounds occurs, it does not do so uniformly in all tissues. Some, such as the intesti-

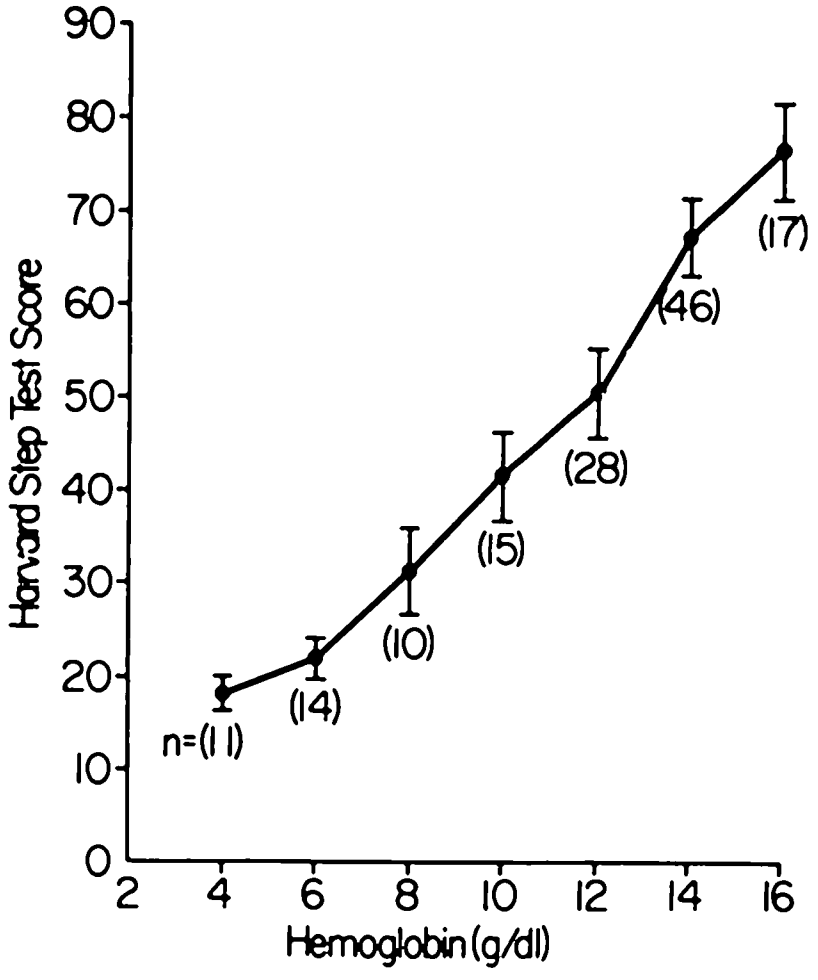

FIGURE 13

The Harvard Step Test score at different hemoglobin concentrations in agricultural laborers living in the lowlands of Guatemala. (Figure from Viteri and Torún.[208] Redrawn with permission).

nal mucosa, are particularly susceptible, while others, such as the myocardium, are much less so. In addition, the rate at which these compounds are repleted in different tissues after the administration of iron is very variable. In cell populations with a rapid turnover, such as intestinal mucosa, restoration of cytochromes takes place rapidly, whereas in skeletal muscle it is very slow.[66,70]

Pathologic and Clinical Significance of Non-Hematologic Sequelae of Iron Deficiency: The translation of findings reported in the previous section into pathologic and clinical terms has not been easy. There is, however, already a persuasive body of evidence indicating that iron deficiency produces a number of deleterious effects in addition to anemia. This evidence relates to muscle metabolism, cell growth, brain metabolism, resistance to infection and temperature control.

Perhaps the best elucidated of these other adverse effects of iron deficiency is *muscle dysfunction*. There is good evidence that iron deficient rats are unable to run properly and that the defect in physical performance is not related to anemia *per se*, but rather to decreased concentrations of the enzyme α-glycerophosphate oxidase in muscle.[112] This enzyme is concerned with the shuttling of

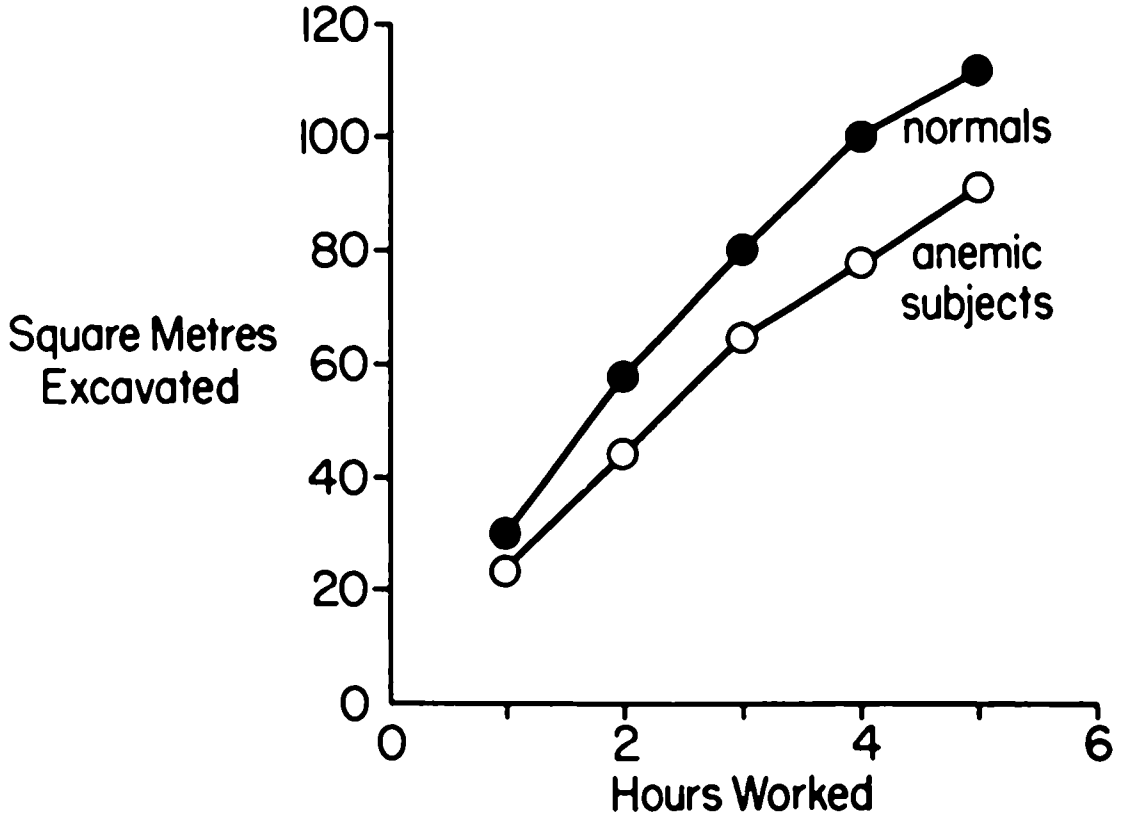

FIGURE 14

Daily work output for normal workers (hematocrit ≥38%) and for anemic workers (hematocrit <38%). The major cause of anemia was iron deficiency. (Figure from Basta and coworkers.[11] Redrawn with permission).

electrons across the mitochondrial membrane, and when its activity is decreased there is an impairment in glycolysis with an accumulation of lactic acid in the muscles (Fig. 15.) It is this increase in lactate levels that impairs muscle activity.[113] While the clinical implications of these findings have not been defined, there are two recent studies that may have relevance. Firstly, the improvement in work capacity that occurred in six adult iron-deficient men and sixteen adult women after the giving of iron treatment could not be totally accounted for by the rise in hemoglobin concentrations.[23] In a second study, blood lactate levels were found to rise considerably higher in iron-deficient subjects than in normal individuals, despite the fact that they were unable to cope with the same work load (Fig. 16).[123] However, interpretation of these latter findings is complicated by the fact that a decrease in oxygen supply secondary to the anemia may have contributed to the lactic acidosis. The need for human trials in which the hemoglobin concentration is eliminated as a variable is therefore a pressing one, since the results have far-reaching implications in relation to the well-being and productivity of large population groups.

Abnormalities in cellular morphology and growth have been described in association with deficiencies of tissue iron compounds. These include structural abnormalities in the liver and myocardium of rats[27,28] and in the erythroblasts and lymphocytes of man.[27] Impairment in the proliferation of red cell precursors[27,124] and lymphocytes[125] has been ascribed to a defect in DNA synthesis, perhaps as a result of inhibition of ribonucleotide reductase[126] and it has been speculated that a similar mechanism may be responsible for the depression in body growth that is evident in experimental

TABLE VI
DEPLETION OF IRON-CONTAINING COMPOUNDS IN IRON DEFICIENCY

Heme Compounds	Myoglobin Cytochromes Catalase Peroxidases
Non-Heme Compounds	NADH dehydrogenase Succinic dehydrogenase Xanthine oxidase Aldehyde oxidase Alphaglycerophosphate oxidase Phenylalanine hydroxylase Ribonucleotide reductase ?
Iron-Dependent Enzymes	Lipid peroxidase Proline hydroxylase Lysine hydroxylase Monoamine oxidase ? Tyrosine hydroxylase ? Tryptophan hydroxylase ?

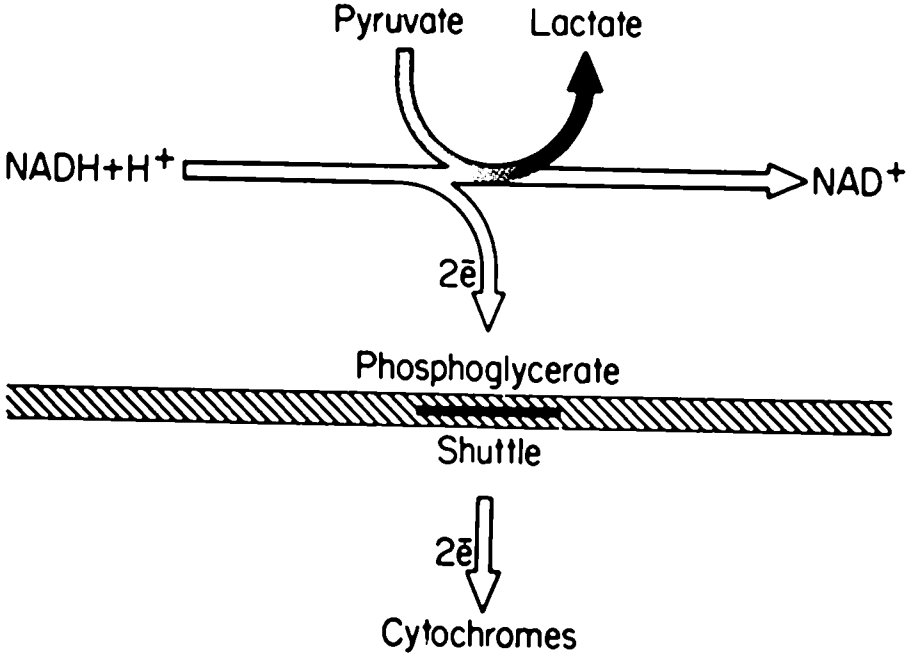

FIGURE 15

An idealized schematic diagram indicating the metabolic block induced by a deficiency of the enzyme α-glycerophosphate oxidase, which shuttles electrons across the mitochondrial membrane.

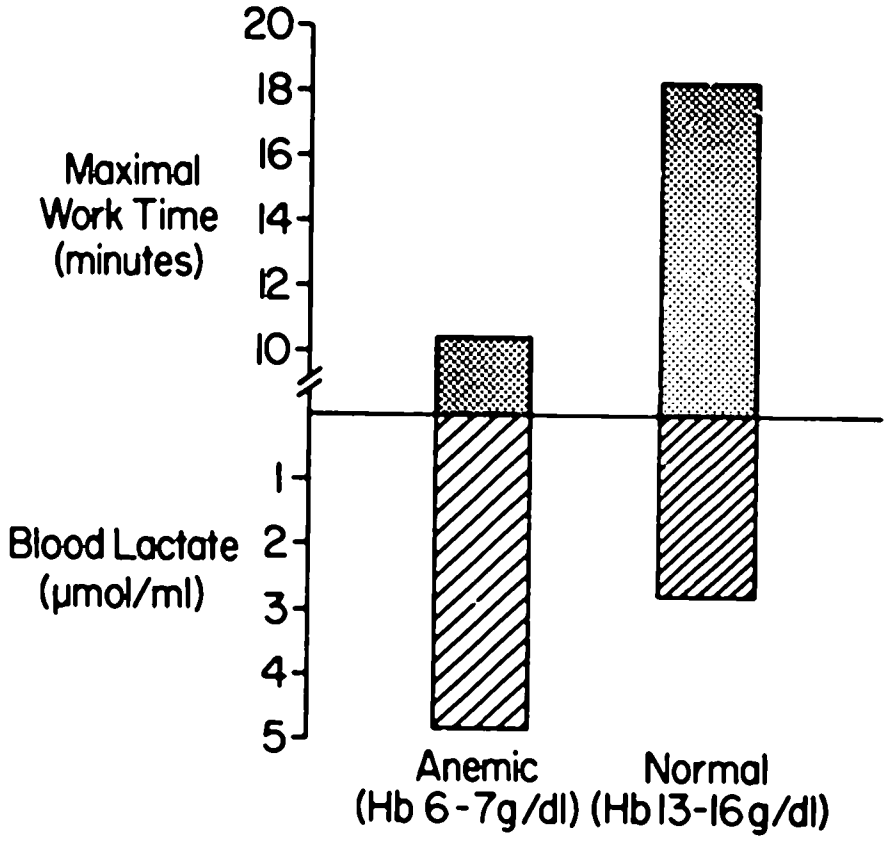

FIGURE 16

Maximum treadmill work time and post exercise blood lactate concentrations in normal subjects and subjects with iron deficiency anemia. (Data from Gardner and coworkers[132]).

animals,[236] and that may possibly also occur in man.[173] Morphologic abnormalities of epithelial structures also occur in association with iron deficiency anemia. These include angular stomatitis, webbing of the esophagus at the cricoid plane and atrophy of the gastric mucous membrane.[3] While it is tempting to relate these changes to the multiple deficiencies of cytochrome enzymes, including cytochrome P 450, that have been noted in iron-deficient experimental animals, their exact significance remains debatable. The prevalence of these manifestations varies so widely that it appears probable that other metal deficiencies and perhaps genetic factors may play a role in their genesis.

The possibility that iron deficiency might cause *abnormalities in brain function* was initially based on clinical observations in children which suggested that they suffered from apathy, irritability and difficulty in concentrating.[210,303,304] However, these studies have been criticized on a number of grounds, and their significance remains conjectural.[197] Perhaps a better documented behavioral disturbance associated with iron deficiency is pica, a compulsion to eat non-food material. Claims that the symptom may be promptly relieved by the administration of iron[47,64,93,242] lend some support to the view that iron deficiency can give rise to this aberration. Limited though suggestive experimental evidence that iron deficiency may, in fact, affect brain metabolism has been obtained in the recent past. Biochemical studies have shown that iron deficiency in early life in the rat causes a depletion in cerebral iron, which persists long after the repletion of other tissues (Fig. 17).[91] The finding of raised levels of serotonin and other 5-hydroxy-indole

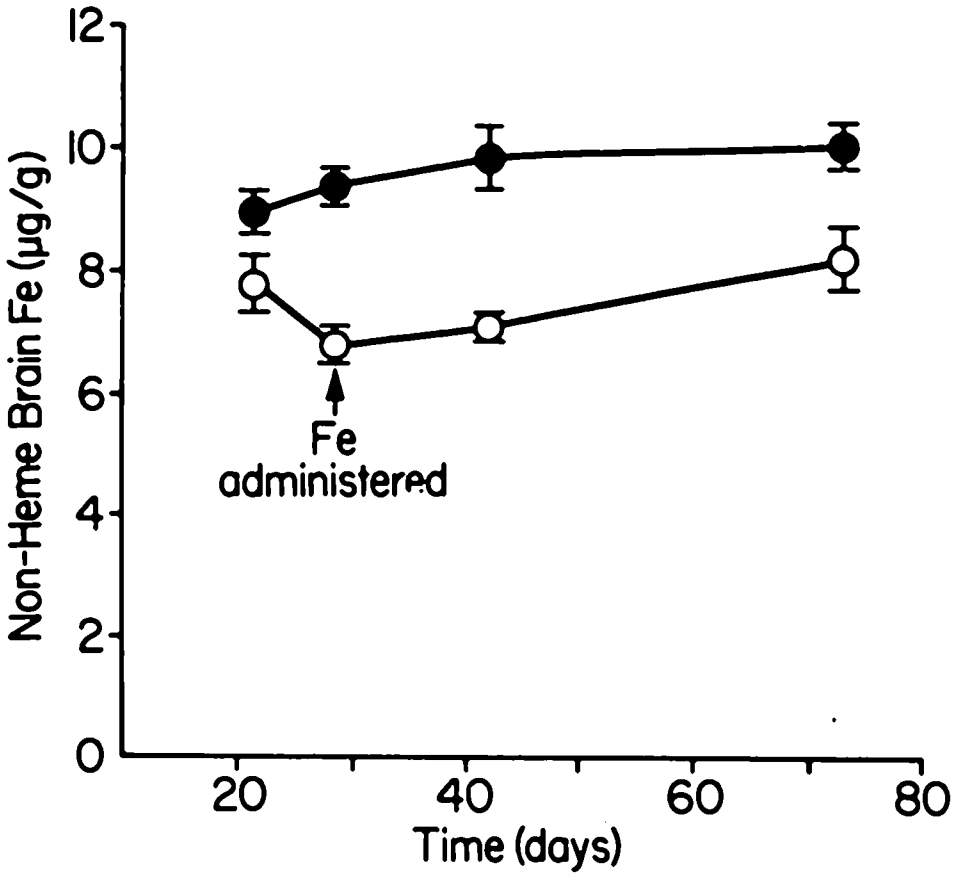

FIGURE 17

Total non-heme iron in the brains of normal and iron-deficient rats are plotted against age. At 28 days of age iron-deficient rats were given intramuscular iron and changed to the control regimen. Standard errors of the means are shown (Figure from Dallman and coworkers[91] Redrawn with permission).

compounds in the brains of iron-deficient rats has been ascribed to a reduction in the concentrations of aldehyde oxidase, an enzyme concerned in serotonin degradation.[41] Interestingly, no decrease in monoamine oxidase, another enzyme concerned with the breakdown of serotonin, was observed, although lower concentrations have been found in platelets of iron-deficient human subjects[91,92] and it has been suggested that a similar deficiency may be present in the brain.[93] The clinical relevance, if any, of these various biochemical observations remains uncertain, since there is not even general agreement on the experimental findings.[37,42,93] At the same time they do raise the possibility of a biochemical link between behavioral disturbances and biochemical abnormalities. Dallman and co-workers' data[91] would suggest that if such a link exists, its impact would be modified profoundly by the developmental status of the brain at the time of the insult.

There is a good deal of experimental evidence suggesting that there is a *decreased resistance to infection* in iron deficiency and that this involves both lymphocyte and granulocyte function. Iron-deficient children have been reported to have a lower percentage of T-lymphocytes,[7,8] impaired lymphocyte transformation[7,8] and a lower incidence of positive skin reactions to common antigens.[8,23,7,8] Granulocyte abnormalities, which include a decreased capacity to kill *E. coli*[23] and *Staphylococcus aureus*,[39] have been ascribed to a

deficiency of the iron-containing enzyme myeloperoxidase[7,140] or to decreased activation of the hexose monophosphate shunt.[223] These changes are rapidly reversed by the giving of iron.[39]. While there are a number of clinical studies which appear to confirm the various experimental findings, firm evidence that iron deficiency is of real clinical significance in this regard is still lacking [illegible] Indeed, there is some reason to believe that iron deficiency may actually have a protective effect against infections. A number of organisms require iron for their growth [illegible] and there is *in vitro* evidence that bacterial growth in plasma is inhibited when the iron concentration is low [illegible] While this effect may be due to the unavailability of iron to the organisms, the presence of unsaturated transferrin may also be important, since this protein has previously been shown to have both anti-viral[114] and anti-fungal properties.[181] In summary, the present findings concerning the relationship between iron deficiency and infection are confused and the subject requires further controlled study.

The role of iron in the *maintenance of body temperature* has only recently been recognized.[97] In contrast to normal rats, iron-deficient rats exposed to a temperature of 4°C are unable to maintain their body temperatures. This is associated with a lower oxygen consumption and a compensatory increased catecholamine drive.[97] The lesion responsible for the inability to maintain body temperature is an impairment in the conversion of triiodothyronine to thyroxine,[98] which is corrected within a few days by the administration or iron. While the relevance of these findings to man remains to be elucidated, they nevertheless point the way to potentially fruitful avenues for future clinical research.

V.
Diagnosis of Iron Deficiency

The initial detection of iron deficiency in an individual is usually made in the laboratory through the recognition of anemia. Once the presence of anemia has been established, tests are then done to establish that it is, in fact, the result of iron deficiency. However, it must be stressed that the hemoglobin concentration varies considerably in normal subjects, so that lesser degrees of iron deficiency will go undetected if it is the only measurement used. The red cell indices help to decide whether the subject is anemic, but for a complete assessment of iron status it is necessary to carry out other tests, to define both the adequacy of the supply of iron to the erythroid marrow (transferrin saturation and free erythrocytic protoporphyrin) and the size of the body iron stores (serum ferritin concentration).

The Definition of Anemia. While it is customary to set arbitrary lower limits of normality for hemoglobin concentrations at different ages in the two sexes, it is appreciated that such figures can only be used as rough guidelines (Table VII). The results of population studies indicate that the distribution of hemoglobin values is Gaussian, with a standard deviation of 10% among apparently normal people, and of about 7% when subjects with iron deficiency are rigorously excluded.[illegible] The distribution curve is skewed to the left in apparently normal populations by the presence of anemic individuals within such populations (Fig. 18).[illegible] When frequency distribution curves of the normal and anemic populations within each total group are plotted, considerable insight can be obtained into the overlap that exists between normal and anemic subjects. This is exemplified by the findings in the pregnant group (Fig. 19). It is apparent that the WHO dividing line of 11 g/dl is an arbitrary one. An additional source of difficulty in this group is the considerable variation in the plasma volume increase that occurs during pregnancy. It is thus apparent that there is no

TABLE VII
HEMOGLOBIN CONCENTRATIONS BELOW WHICH ANEMIA IS LIKELY TO BE PRESENT IN POPULATIONS LIVING AT SEA LEVEL*
(Data from WHO Technical Report Series No. 405[illegible])

	g/dl
Adult males	13
Adult females (non-pregnant)	12
Adult females (pregnant)	11

*Modification for altitude 0.3 g/dl for each % decrease in oxygen saturation. (Data from Hurtado[illegible])

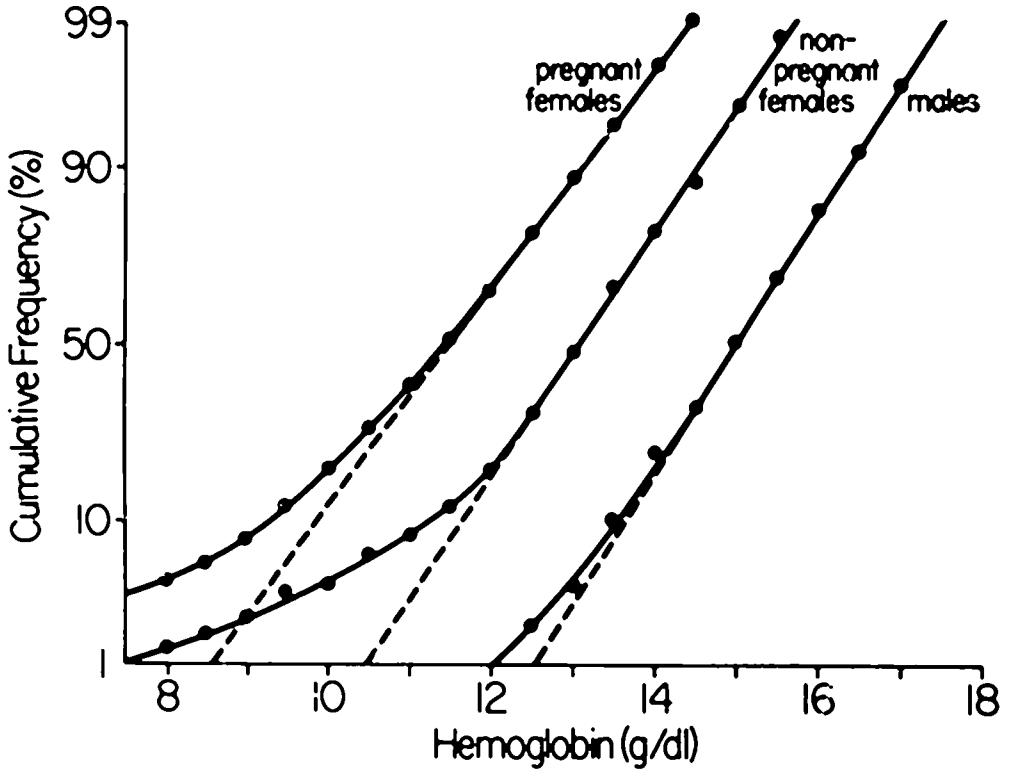

FIGURE 18

Probability plots of cumulative frequency distributions for hemoglobin concentrations in pregnancy, in non-pregnant females and in male subjects living in Latin America. It can be seen that the upper portions followed a linear pattern typical of a single Gaussian distribution. Deviation from this plot was minimal in males but was noted in both non-pregnant and pregnant females. There was therefore a double population of hemoglobin values in both female groups. Among non-pregnant females 88% were contained in the upper population (mean hemoglobin 13.1 g/dl) and 12% fell in the lower distribution (mean hemoglobin 10.6 g/dl). Corresponding figures in the third trimester of pregnancy were 78% (mean hemoglobin 11.8 g/dl) and 22% (mean hemoglobin 9.8 g/dl) respectively. [After Cook and coworkers.[40] Redrawn by permission of the Editor, *Blood* (38:591, 1971)]

magic figure dividing normality from abnormality, and that while a particular cut-off value can be used to determine the approximate prevalence of anemia in a population, the reliability with which it can identify the anemic individual is a matter of probability, based on the distribution curve of hemoglobin values in a representative sample of healthy female subjects. (How such samples can be obtained has been discussed in some detail in a WHO report).[119] Obviously the probability of anemia being present increases as the hemoglobin concentration drops (Fig. 20). A non-pregnant female with a hemoglobin concentration of 11g/dl has a 20% chance of being normal, the apparently anemic value representing in fact her physiologic norm.

When attempting to assess the significance of a particular hemoglobin concentration in the individual case, it is important to get information on the morphologic characteristics of the red cells. Since electronic counters measure the size of the red cells and the hemoglobin concentration accurately and directly, the two indices that are of most use are the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin (MCH). They represent

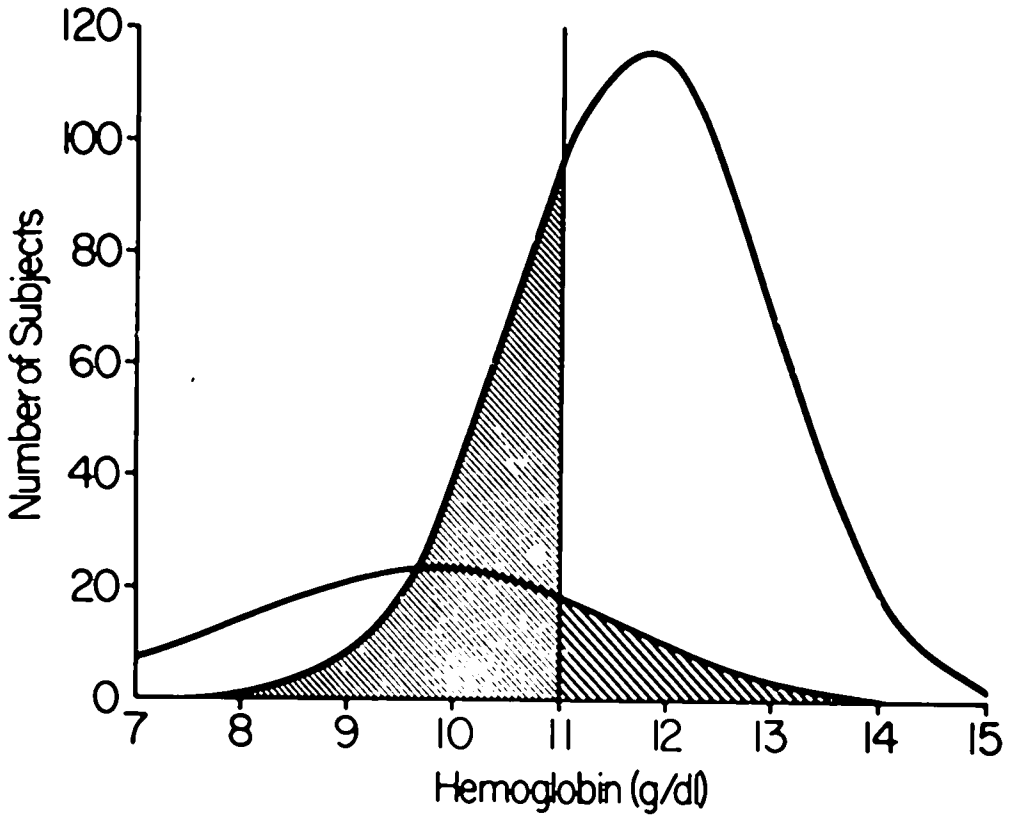

FIGURE 19

Fitted double population of hemoglobin concentrations in the third trimester of pregnancy in Latin American women. The vertical line depicts the hemoglobin value used to define anemia according to WHO criteria. The higher curve represents the distribution of the normal population of pregnant women and the lower curve, the anemic group (see previous fig.). The cross-hatched area above 11 g/dl represents subjects found anemic by distribution analysis but considered normal by WHO criteria. The shaded area below 11 g/dl represents that portion of the population found normal by distribution analysis but considered anemic by WHO criteria. [After Cook and coworkers.[44] Redrawn by permission of the Editor, *Blood* (38 591, 1971)]

reliable diagnostic indicators of iron deficiency anemia, except in those situations where there is a dimorphic population of small and large cells (e.g. combined iron and folate deficiency). Electronic counter measurements have made it possible to follow the sequence of events as the erythroid marrow is progressively deprived of iron. An increase in the percentage of microcytes is the most sensitive index (Fig. 21),[115] and the MCH and MCV decline in parallel with the hemoglobin concentration until eventually the full blown picture of a microcytic hypochromic anemia is apparent.

The finding of an anemia together with a low MCV (<85fl) and a low MCH (<27pg) usually implies that hemoglobin synthesis has been inhibited by a curtailment in the supply of iron to the erythroid marrow, usually due to true iron deficiency. The inadequate iron supply can, however, also be caused by an impairment in the release of iron into the plasma from the reticuloendothelial system, and this may be found in a variety of chronic disorders.[32] Impaired hemoglobin synthesis resulting in similar morphologic changes occurs in thalassemia minor, and in areas where the disorder is common, such as the Mediterranean region and Southeast Asia, this possibility must always be taken into consideration. While other measurements, such as the concentrations of fetal hemoglobin and hemoglobin A_2, may be necessary

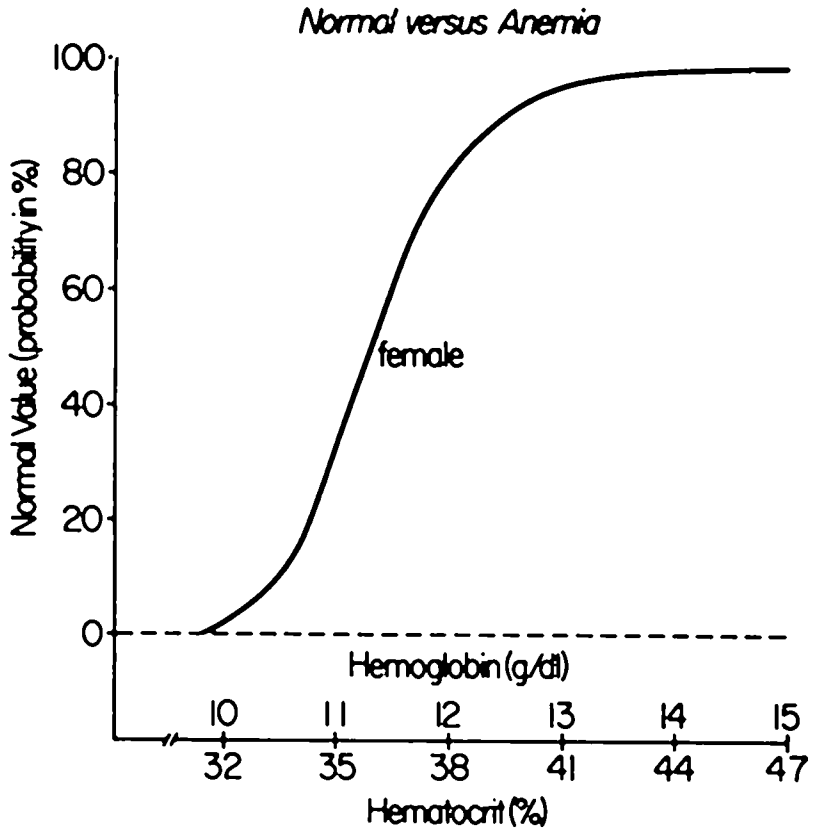

FIGURE 20

The distribution of hemoglobin values in a theoretical population of women with a mean value of 13.5 g/dl (SD ± 1 g/dl) and an assumed 10% prevalence of anemia. For each hemoglobin concentration the likelihood that it is normal in the individual tested may be read on the vertical axis (Data from Hillman and Finch[18]).

for differentiation of the two conditions,[26] simple discriminant formulas using blood indices have been found useful. One example is as follows: - Discriminate function = MCV - RBC - (5 × Hb) - 3.4. If the result is positive the diagnosis is iron deficiency, while a negative result suggests thalassemia trait.[17,18]

Iron Deficient Erythropoiesis. Two measurements are useful for assessing the adequacy of the iron supply for hemoglobin synthesis. These are the percentage saturation of the plasma iron-binding protein, transferrin, and the red cell protoporphyrin concentration. When there is not enough iron entering the plasma, the plasma iron concentration falls progressively from its normal levels (mean 115 μg/dl, SD ± 40 μg/dl) and when it is less than 40 μg/dl it is probable that the needs of the erythroid marrow are not being adequately met. However the adequacy of iron supply to the marrow correlates better with the percentage saturation of transferrin, which decreases in parallel with the plasma iron concentration. This decrease is due not only to the lowered plasma iron concentration, but also to a concomitant increase in the amount of transferrin.[12] The normal mean plasma iron-binding capacity is about 330 μg/dl (SD ± 25 μg/dl); in iron deficiency the extra transferrin usually raises it to between 370 and 580 μg/dl.[17,18] Why this should be so is not known, but together with the lowered plasma iron concentration the consequence is that the transferrin saturation drops from its normal value of 30%-40% to low levels. Once it has fallen below 15%, the delivery of iron to

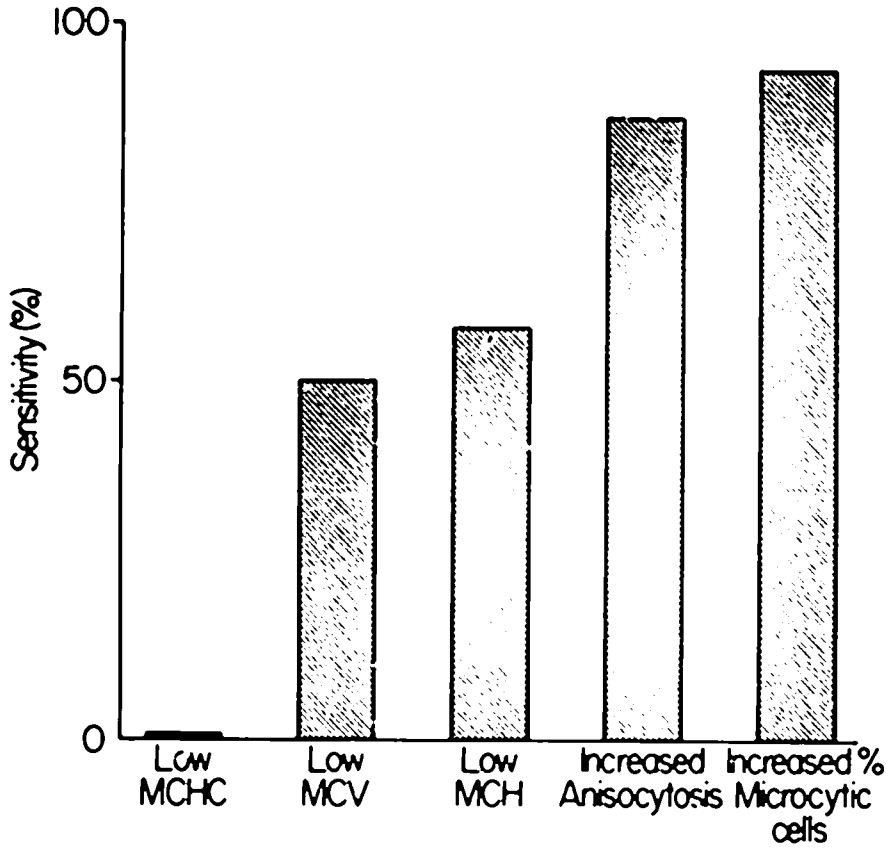

FIGURE 21

The sensitivity of various hematologic measurements in detecting blood donors with low transferrin saturations (<16%). (Data from England and coworkers[111]).

the erythroid marrow is severely compromised.[8] When the supply of iron to the developing red cells in the marrow is suboptimal,[8,29] not all the porphyrin being synthesized can be made into heme.[86,193,197,204,292,299] As a result, the concentration of protoporphyrin in the circulating red cells rises above normal. The normal figure for free erythrocytic protoporphyrin is about 40 μg/dl red cells, or somewhat less than 1 mole per 20,000 moles of heme. If the figure is greater than 70 μg/dl red cells, the iron supply to the erythroid marrow can be regarded as suboptimal.

Assessment of the Iron Reserve. The most convenient yardstick of the body iron reserve is the plasma ferritin concentration, since it can detect the first stage of iron deficiency, namely a reduction in the size of the stores. There is now abundant evidence that the plasma ferritin concentration bears a linear relationship to the body iron stores[29,199,201] and it therefore provides an invaluable guide to the iron nutritional status. It has been employed for both clinical and epidemiologic purposes. Each μg ferritin/l plasma is equivalent to about 10 mg storage iron, while figures lower than 10-12 μg/l indicate virtual exhaustion of the body iron stores.[21,126,199,321] In a recent epidemiologic study, a survey was carried out in normal men and women in the United States (Fig. 22).[32] In females, values stayed low until the menopause, at which time they began to rise, presumably as a result of the cessation of the menstrual iron drain. In males, there was a steady build-up in ferritin concentrations throughout adult life. Since the figures in later life suggest iron stores somewhat greater than those found in necropsy studies,[62] it is possible that other

factors may have modified them. In this connection, it is noteworthy that there are a number of disease states in which falsely high plasma ferritin concentrations may be found, including liver disease, leukemias, lymphomas, cancers and infection.[221] However, there is no condition other than iron deficiency in which it is reduced to very low levels and a plasma ferritin concentration below 12 μg/l implies that stores are exhausted or almost exhausted. Information similar to that provided by the plasma ferritin concentration can be obtained more directly by histologic examination of the bone marrow for hemosiderin granules in the reticuloendothelial cells.[22] While this traditional and well-tried method of assessing the size of the body iron stores is still useful in the clinical work-up of individual patients, it is not suitable for epidemiologic studies.

In summary, therefore, the most useful tests for the evaluation of iron nutrition are the plasma ferritin concentration, the percentage saturation of the plasma transferrin, the red cell protoporphyrin concentration and the hemoglobin concentration. Current concepts concerning the relationship of these various measurements to each other and to other indices at various stages of iron depletion are shown in Fig. 23. For the mildest degree of iron deficiency, amounting to a reduction in the body iron reserve only, the plasma ferritin concentration provides the only convenient yardstick. Once the deficiency of iron is of sufficient severity to compromise the supply of iron to the bone marrow, this is most conveniently assessed by a fall in the percentage transferrin saturation and a rise in the red cell protoporphyrin concentration. A raised red cell protoporphyrin concentration indicates that

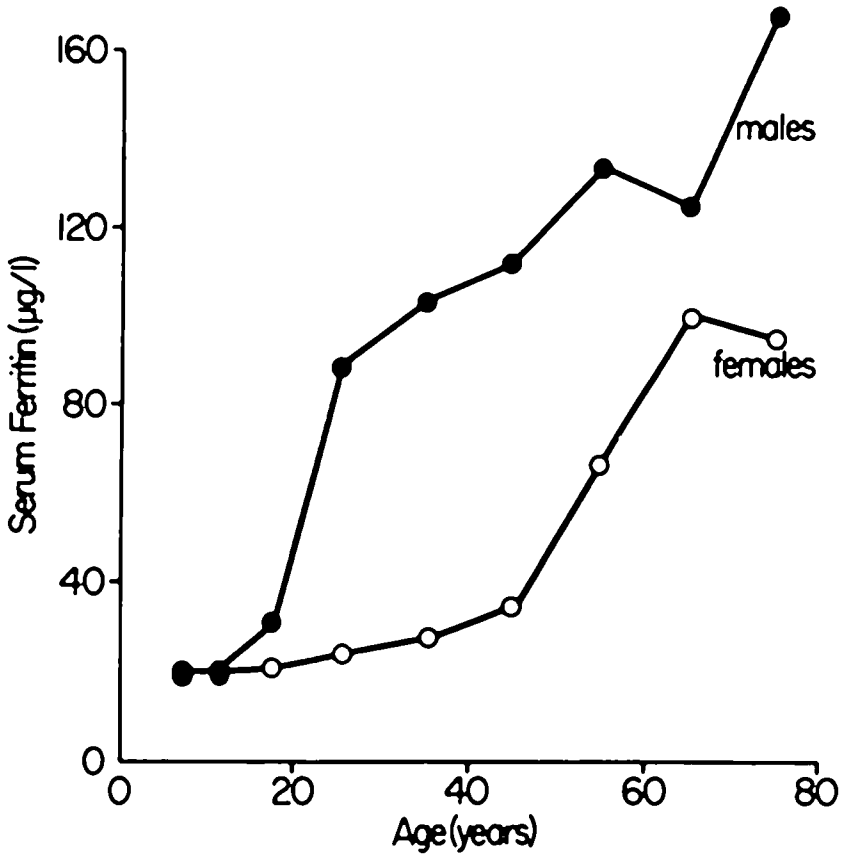

FIGURE 22

Median values for plasma ferritin concentrations in male and female subjects of different ages. [Data from Couk and coworkers.[71] Redrawn by permission of the Editor, *Blood* (48:449, 1976).]

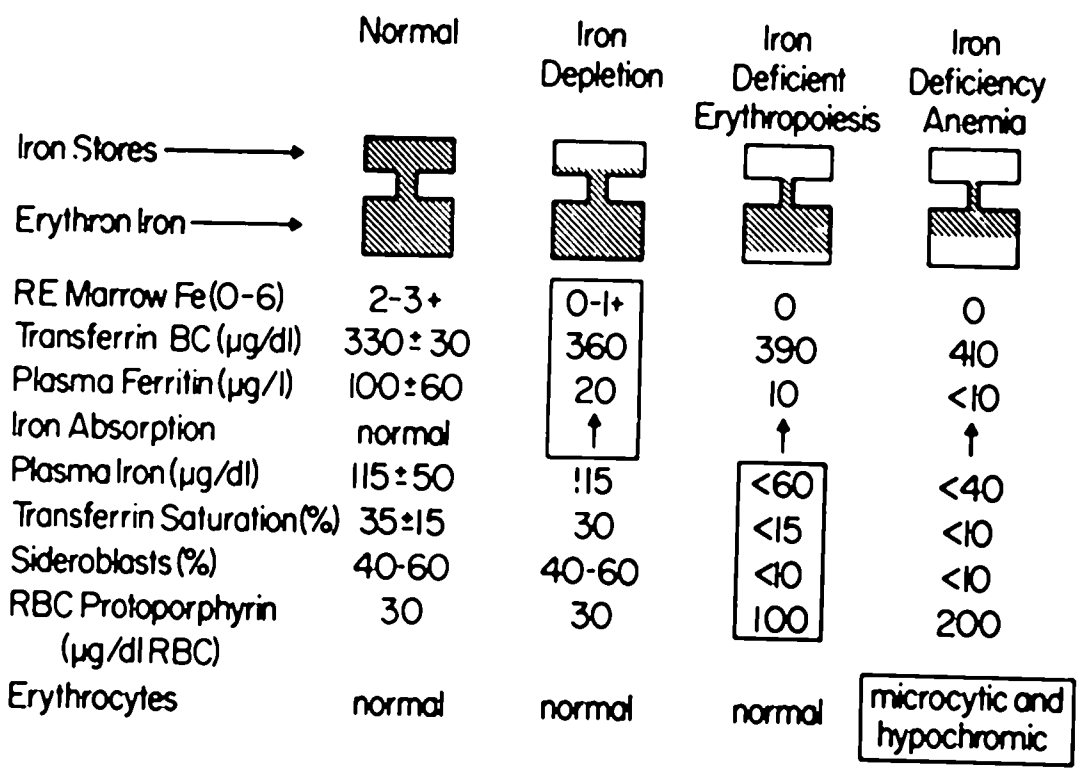

FIGURE 23

The sequence of changes induced by a gradual reduction in the iron content of the body (Reproduced with permission from *Iron Metabolism in Man*[37]).

less hemoglobin is being synthesized than normal. That the inadequate supply of iron for hemoglobin synthesis is due to true iron deficiency rather than defective release of iron to the plasma, as occurs in a number of chronic disorders, can be confirmed by a low plasma ferritin concentration, or by the absence of stainable iron in the bone marrow. Changes in the red cell indices require iron deficiency of fairly marked degree which has been present for long enough for a significant proportion of the red cell population to exhibit the characteristic morphologic features.

The differentiation between true iron deficiency and a restricted supply due to chronic inflammation and other chronic disorders[37] is made on several grounds. With infection, the total iron-binding capacity is often reduced rather than raised, the percentage saturation is normally below 15% and most importantly, the plasma ferritin concentration is usually above 100 μg/l.[24,120,122,123] When there is concomitant iron deficiency, the plasma ferritin is between 20 and 50 μg/l. Differentiation from defects in porphyrin and globin synthesis is not difficult, since the plasma ferritin concentration is normal or raised, while both the transferrin saturation and the red cell protoporphyrin are normal.

Assessment of Iron Status of a Population: Since the sensitivity and specificity of the four measurements of iron status vary widely, attempts have been made to use them in an integrated way in order to define more precisely the iron nutrition of population groups. This information is particularly necessary in evaluating the effectiveness of iron

supplementation and fortification programs.[319,320] In the past it has been customary to determine the percentage of values outside the normal range. When this was done in one study it was found that if only one of the measurements was in the iron deficient range, the prevalence of anemia was only slightly higher (10.9%) than in the population as a whole (8.3%).[72] When two were abnormal, the prevalence of anemia rose to 28% and when all three were abnormal it was 63%. It is, however, difficult to relate such figures to other populations, since they must be influenced by the prevalence of other causes of anemia.

In one recent study an attempt was made to give weighting to each of the measurements of iron status in order to estimate the distribution of iron stores in a particular population.[71] In this model (Fig. 24) four grades of iron nutritional status are recognized.

1. All measurements are *normal*. The body iron reserve in this group is obtained by assuming that each 1 μg ferritin/dl plasma is equivalent to 10mg storage iron. This is, in fact, the calculated weighted mean for this relationship as obtained in several studies.[74,170,301,321] [Calculated stores (mg) = plasma ferritin (μg/l) × 10].

2. *Storage iron depletion* is present when the plasma ferritin concentration is less than 12 μg/l. In an attempt to obtain further precision it was assumed that if the hemoglobin concentration was above 12g/dl and one of the other two measurements (transferrin saturation or red cell protoporphyrin) was abnormal, then no storage iron was present.

3. *A latent hemoglobin iron deficit* is present when the findings are similar to 2, except that the transferrin saturation *and* the red cell protoporphyrin are in the iron deficient range. This is assumed to imply a hemoglobin iron deficit of 150mg.

4. *An overt hemoglobin iron deficit* is present when the hemoglobin concentration is less than 12g/dl. The deficit can be calculated on the assumption that 1g/dl hemoglobin in a 70kg woman is equivalent to 150mg iron. If the hemoglobin concentration in a normal woman is taken to be 14g/dl, then one of 11-12g/dl represents a hemoglobin iron deficit of 300mg, one of 10-11g/dl a deficit of 450mg, and so on.

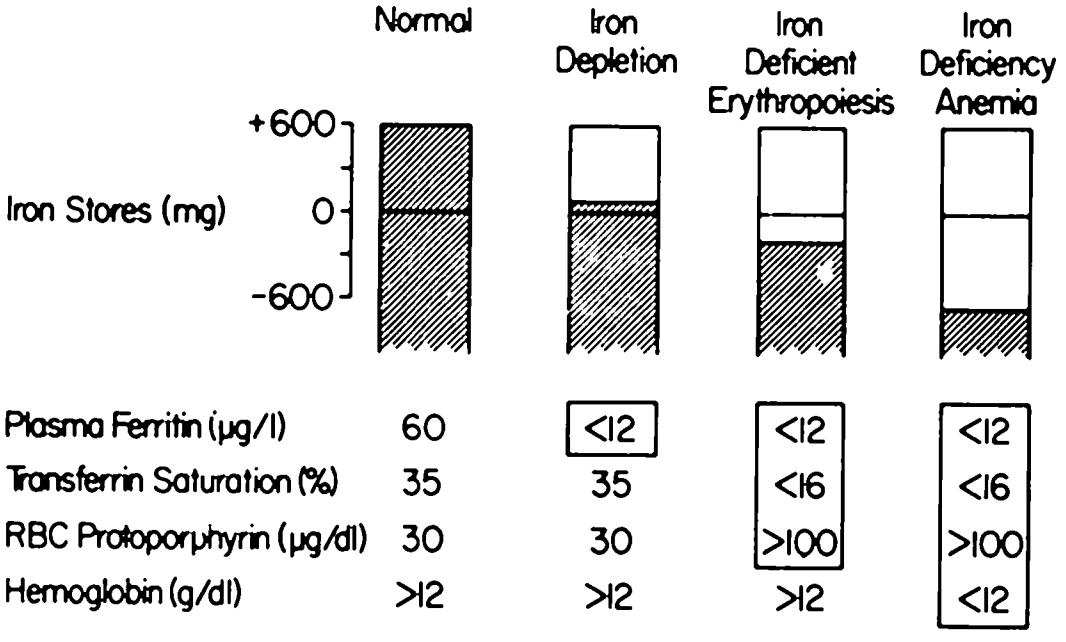

FIGURE 24

Measurements of iron status in relationship to body iron stores (mg). Negative iron stores indicate the amount of iron that must be replaced in circulating red cells before iron reserves can re-accumulate. (Data from Cook and Finch.[71] Redrawn with permission).

Using these various assumptions, a cumulative frequency distribution of iron stores was constructed on data obtained in an epidemiologic study that had been carried out on 426 women in the Northwestern United States (Fig. 25)[24] The median store of iron was calculated to be 220mg with lower and upper tenth percentiles of 240mg and 700mg respectively

While it is apparent that the model gives plausible results, it is based on a number of assumptions, the chief of which is the quantitative nature of the relationship between the plasma ferritin concentration and the size of the body iron stores. Results obtained with the model should therefore be treated with caution until it has been tested further. In this regard, it will be of interest in the future to evaluate the effect of iron supplementation and fortification strategies not only on each of the measures of iron status but also on the cumulative frequency distribution of iron stores as calculated from the individual measurements In addition, in such studies it will be important to evaluate the effect of iron fortification of the diet on the iron-replete male population, since the possible risk of iron overload has excited spirited debate in developed countries.[21]

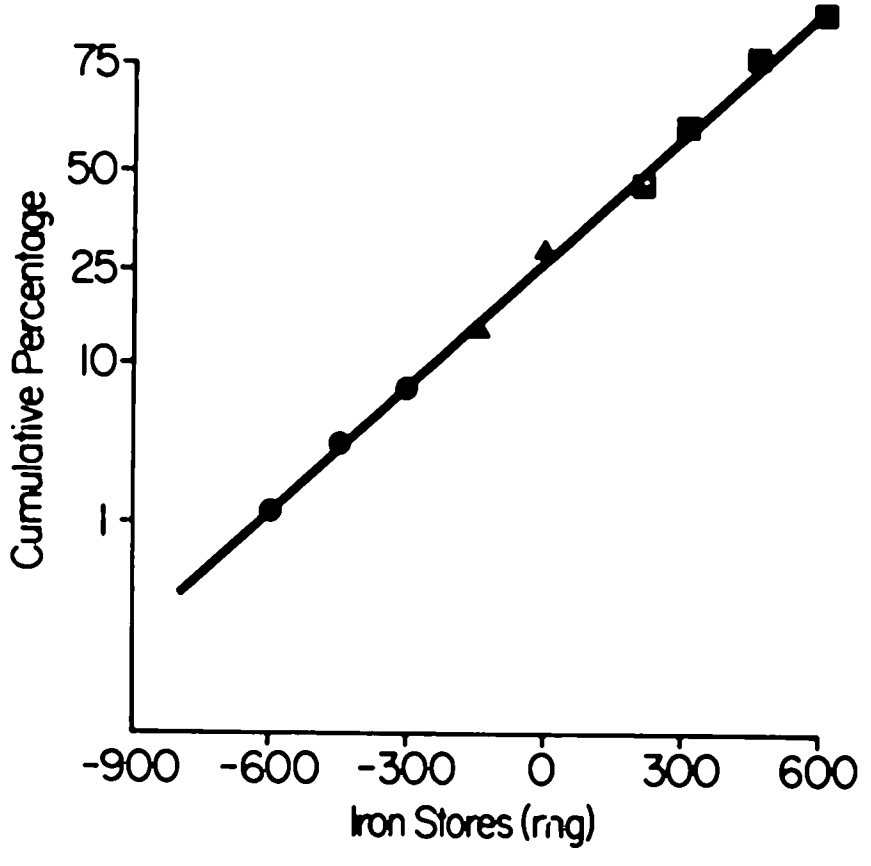

FIGURE 25

Cumulative frequency distribution of iron stores in 426 women In various regions of the curve, the points were derived from serum ferritin, (■) transferrin saturation and or free erythrocyte protoporphyrin (▲), and hemoglobin concentration (●) as described in text (After Cook and Finch [24] Redrawn with permission)

VI.
Prevention of Iron Deficiency

Nutritional iron deficiency can be prevented either by identifying the vulnerable members of the population and providing them with iron supplements, or by fortifying the diet with iron so that the iron nutrition of the whole population is improved

Iron Supplementation

Supplementation involves the giving of iron in medicinal form This is often the only feasible approach when there is a large iron requirement and a relatively short time span, as occurs during pregnancy [illegible] The prevalence of anemia during the third semester as judged by [illegible] detection of a hemoglobin concentration less than 11g/dl has been studied in a number of countries during the last several years [illegible] While the samples tested were mostly women from the lower socio-economic strata who were attending hospitals and antenatal clinics, and were thus not necessarily representative of the whole population, the prevalence of anemia in the selected groups was extremely high in a number of countries (Table VIII).

Although other deficiencies, and especially folate deficiency, were probably contributory factors to the anemia in many areas, it is noteworthy that a transferrin saturation of less than 15% was present in between 40% and 50% of the women studied.[13] These figures therefore underline the need for iron supplementation during pregnancy,[illegible] and also indicate that there are many areas of the world where it should be given together with folate supplementation In this context, it must be stressed that while the need for supplemental iron is greatest in developing areas, it also exists in affluent societies. The point was underlined by a study carried out in Sweden by Svanberg and co-workers (1975) There was a progressive fall in the hemoglobin concentration and hematocrit in a group of women given a placebo (Fig 26) This was accompanied by a fall in the plasma iron concentration and a rise in the total iron-binding capacity, with the result that there was a steady drop in the transferrin saturation (Fig 27) These changes were significantly less in those treated with 200mg ferrous iron daily. By mid preg-

TABLE VIII
PERCENTAGE OF PREGNANT WOMEN IN THIRD TRIMESTER WITH HEMOGLOBIN CONCENTRATIONS LESS THAN 11 g/dl.
(Data from Baker and DeMaeyer[illegible])

Poland	22	India	
Latin America		-Vellore	56
(7 countries)	25	-Delhi	80
Venezuela	37	Israel	47
Mexico	27	Burma (Rangoon)	84

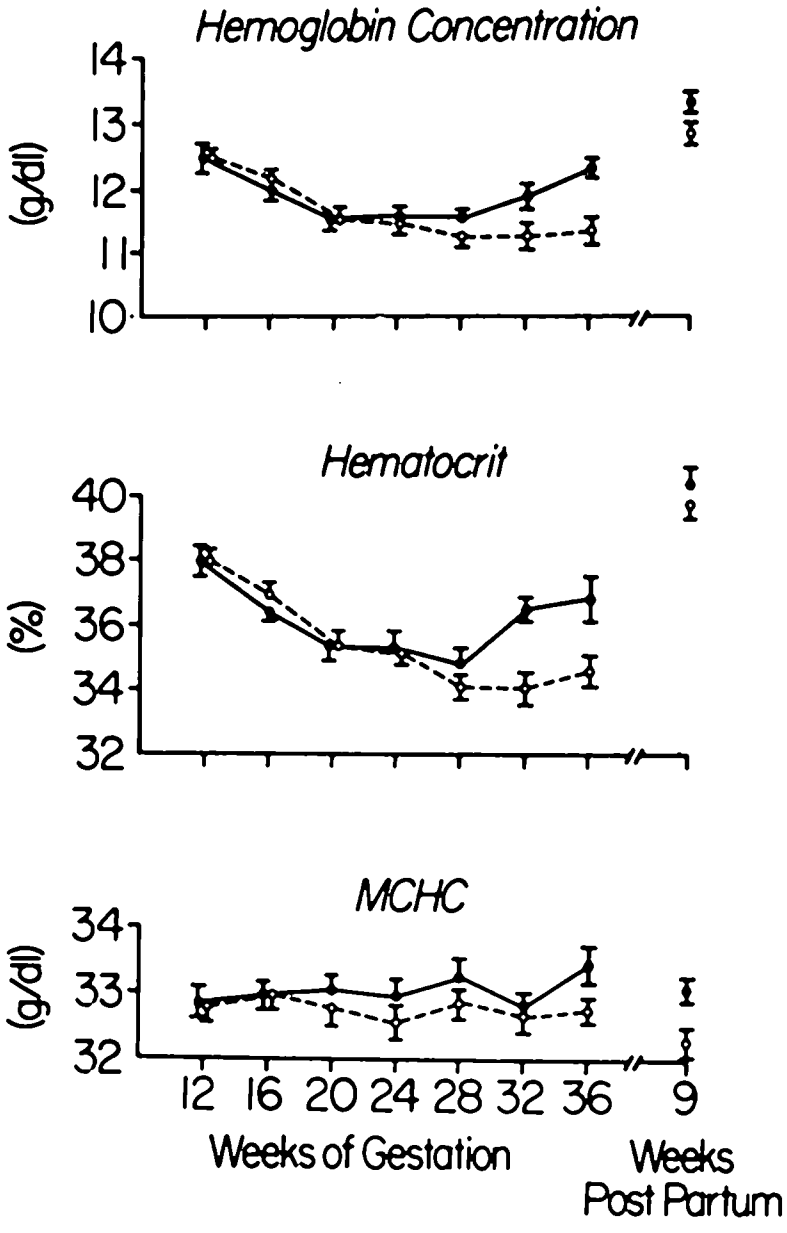

FIGURE 26

The mean (±SE) hemoglobin concentration, hematocrit and MCHC in pregnant women treated with a placebo (open circles) or 200 mg ferrous iron (black circles) daily. (After Svanberg and coworkers[502]).

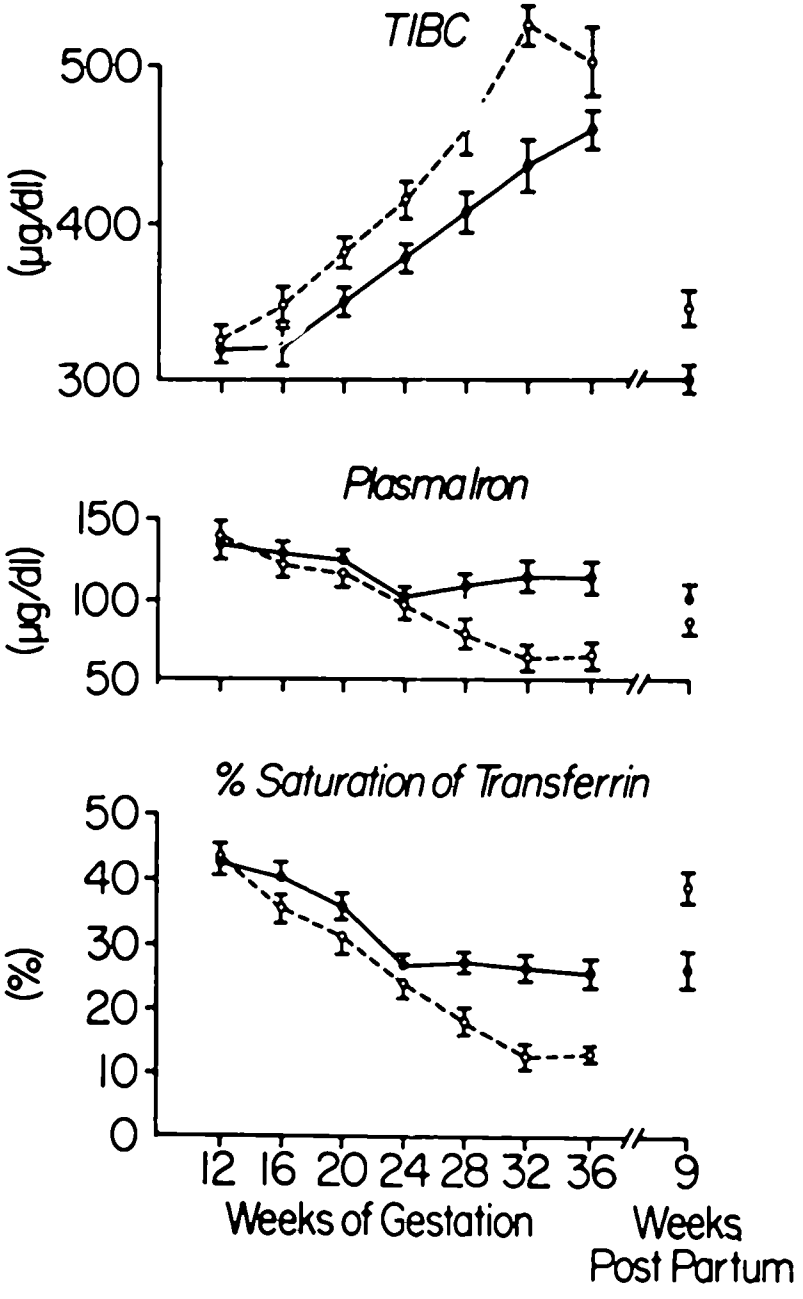

FIGURE 27

The mean (±SE) total iron-binding capacity, plasma iron concentration and percentage saturation of transferrin in pregnant women treated with a placebo (open circles) or 200 mg ferrous iron (black circles) daily (After Svanberg and coworkers[142]).

nancy there was a modest drop in the hemoglobin concentration and hematocrit but they rose again towards the end of pregnancy. The plasma iron concentration remained virtually unchanged throughout pregnancy but there was some drop in the transferrin saturation. This was due to the fact that the total iron-binding capacity, which reflects the amount of circulating transferrin, rose steadily throughout pregnancy. The rise was presumably the result of some hormonal change and was not due to iron deficiency. Further insight into changes occurring during pregnancy was obtained in a study in which the plasma ferritin concentration was measured at various stages of pregnancy (Fig. 28).[114] In women not receiving iron supplements there was a progressive fall from the twelfth week onwards to a mean figure of 13μg/l at term. This fall presumably reflected the mobilization of iron from stores. In contrast, a group receiving 90mg ferrous iron daily still had a mean plasma ferritin value of 50μg/l at term.

Some guidelines as to the dosages of supplemental iron required have been obtained in studies in which iron absorption has been measured at various stages of pregnancy. In one study, the absorption of a small dose of ferrous iron (0.56mg) was measured at various stages of pregnancy. There was little change in absorption during the first trimester, with a dramatic increase occurring during the second and third trimesters (Fig. 29). Somewhat different results were obtained by Svanberg and co-workers in a study in which they measured the absorption of a 30mg dose of ferrous iron when fed together with a standard meal of 4690kcal at various stages of pregnancy. Absorption was actually *depressed* during the first trimester from a normal mean figure of 7.2% to 1.5%. In the second trimester it was 5.8% and only in the third trimester did it rise to 14.6%. Recent data suggest that in developed countries there is an increase in energy intake during pregnancy from about 1700kcal per day to 2100kcal per day. Since the iron content of Western-type diets is surprisingly constant at 6mg/1000kcal,[29,30] this represents a total intake of 12.6mg daily, including 0.75mg heme iron of which 33% would be expected to be absorbed. Calculations based on all three data suggest that the

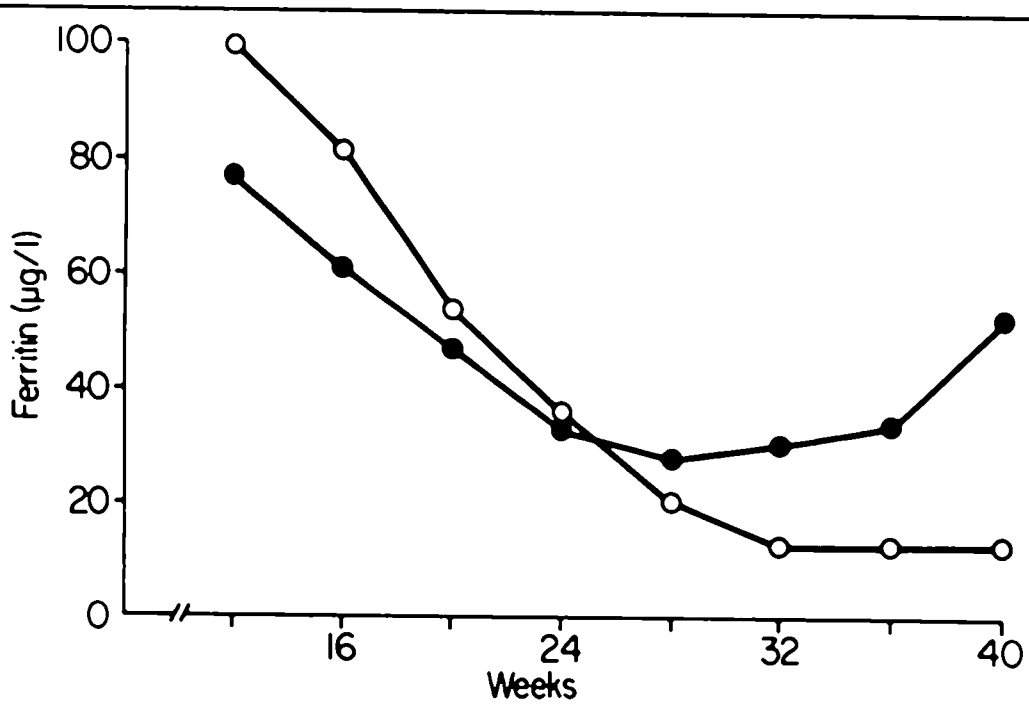

FIGURE 28

Plasma ferritin concentration in two groups of pregnant women. The one group (open circles) was not given an iron supplement, while the other (black circles) was given 90 mg ferrous iron daily. (Data from Fenton and coworkers[114]).

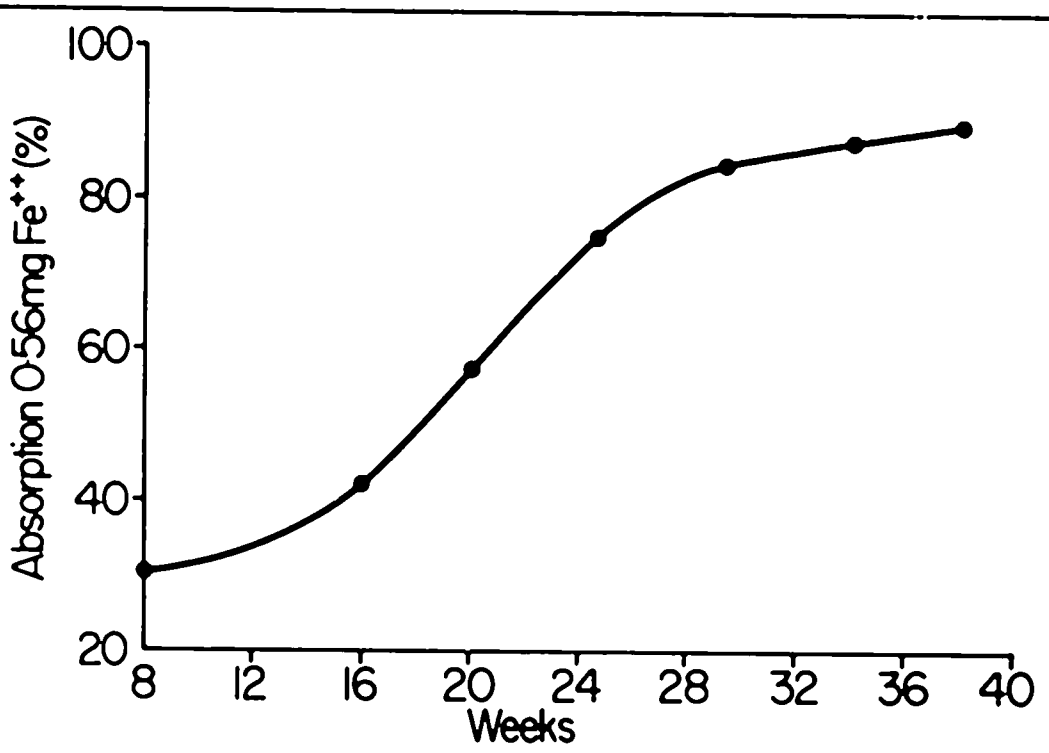

FIGURE 29

The changes in iron absorption that occur in pregnancy (Data from Heinrich and coworkers[136]).

total daily iron absorption for the three trimesters from a diet supplemented with 30mg ferrous iron would amount to 0.9mg, 2.7mg and 6.5mg respectively. While certain assumptions have been made in these calculations, the figures do suggest that the 30mg daily iron supplement given with food in Svanberg and co-workers' study[75] was not really sufficient to meet the needs of pregnancy, and this was especially so during the second trimester. Were the supplemental iron to be given *between* meals rather than *with* meals, absorption would be expected to be almost twice as great,[42] but compliance would be less, since it is easier for subjects to remember to take the prescribed iron at mealtimes than in between meals. Poor compliance is by far the likeliest explanation for the failure of a prophylactic regimen or course of treatment with an iron preparation. In one study only 68% of a group of pregnant women were found to be taking their iron supplements as ordered, and of those whose hemoglobin concentrations were lower than 12g/dl at term, only 25% were doing so.[34]

In practical terms the actual daily dosage of supplemental iron required during pregnancy is affected by a number of considerations. In populations where the prevalence of iron deficiency is high there are many women who enter pregnancy already suffering from various degrees of anemia. In such a situation full therapeutic doses of a well absorbed iron salt are obviously needed. On the other hand, in many developed countries most women enter pregnancy not only with normal hemoglobin concentrations but also with a reserve of iron of 200 to 300mg. The supplementation required in such instances is less, since all that is really required is a daily dose of iron sufficient to meet the increased needs of pregnancy, which in the second and third trimesters reach figures of about 5 to 6mg daily. This should preferably be given once daily with a meal, to ensure maximum compliance. In Scandinavian countries most non-anemic women are given 100mg daily as ferrous sulfate (slow release) from mid-pregnancy until term. The rationale for this dosage schedule is as follows: in the antenatal clinic it is often difficult to know whether a particular woman is iron-deficient or not, since only a hemoglobin estimation is usually carried out. In such circumstances, it seems reasonable to choose a supplementation dose suffi-

cient to meet the needs of pregnancy and to correct minor degrees of iron deficiency. An alternative approach is to administer a smaller daily dose of iron (40 to 60mg) as a simple ferrous salt on the basis that compliance is adversely affected by side-effects and that side-effects are dose-related.

While supplementation has a major role to play in developing countries where iron deficiency is common, there are many areas in which the dosage schedules recommended in Western countries do not apply. This can be ascribed to the fact that a large number of women enter pregnancy not only without a storage iron reserve, but also with a hemoglobin deficit. In addition, they may only present themselves in the latter part of pregnancy, so that a limited time is available for intervention. This was well illustrated by two studies which were carried out in India.[232,233] In the first of these studies, varying doses of iron as ferrous fumarate were given under supervision on a once daily basis for twelve weeks, with most of the women also receiving supplemental folate and vitamin B_{12}.[232] The best results were obtained with a single daily dose of 240mg, but even in this group the hemoglobin concentration did not rise above 11g/dl in 50% of the women. These results were explained on the basis that the total daily needs during the period of supplementation amounted to 15mg, which was more than would be expected to be absorbed from a single daily dose of iron.[229,232] In a second study, a daily dose of 120mg iron per day as ferrous sulfate (Fersolate, Glaxo Laboratories, India) for 10 to 12 weeks caused a mean rise in the hemoglobin concentration of 1.12g/dl in a group of pregnant Indian women at 26 ± two weeks of gestation. Calculations based on these data suggested that only 3.24mg of the administered iron had been utilized daily for hemoglobin production as compared with a figure of 5.18mg when repeated injections of intramuscular iron-dextran (Imferon, Tata Fison, India, Ltd) were given.[233] While the reason for the relative malabsorption of iron in these women was not elucidated, the results do underline the dangers in extrapolating the findings from one country to another. If an iron supplement is to be used, its effectiveness must be tested under field conditions in a representative sample of the group to whom it is going to be given. It is only in this way that a correct dosage schedule can be ensured.

While parenteral iron represents an effective alternative to oral iron in those areas where the required daily supplemental dose during pregnancy is large, it is really not a practical proposition, since such preparations are expensive and may cause severe reactions. The current need is for some stable form of oral iron that can be given on a once daily basis, which is well absorbed and yet does not have unpleasant side-effects.[133] It has been calculated that if a 50kg woman presents at 24 weeks of pregnancy with a hemoglobin of 8g/dl, her total iron requirement for the remainder of pregnancy is approximately 1250mg. This means that if she is to be treated over a 100-day period, she needs to absorb 12.5mg daily.[133] While it is possible to achieve this by feeding a single daily supplement of about 175mg iron in the form of a soluble ferrous salt, a proportion of individuals can be expected to experience gastrointestinal side-effects at this dosage level.[234] When such side-effects occur, many women stop taking the tablets and may even stop attending antenatal clinics. Alternative approaches therefore seem warranted. One alternative currently being considered is the use of one or other of the controlled-release preparations, which might be expected to have fewer side-effects. While the relative efficiency of several of the preparations currently available on the market has not been adequately documented, at least one of them has been shown to be absorbed to the same degree as ferrous sulfate when given in the fasting state and 30% better when given with food.[132,233] In addition, it produces significantly fewer side-effects.[233] The major current challenge is to develop effective preparations at costs which are competitive with those of conventional iron compounds.

Iron Fortification

The term "fortification" is used to describe "the process whereby nutrients are added to foods to maintain or improve the quality of the diet of a group, a community or a population."[218] It is an approach which can be applied to large population groups at low cost, and it has the advantage that the identification and cooperation of actually or potentially deficient individuals is not a prerequisite as it is with supplementation. There are, however, many practical and theoretical problems relating to fortification programs. This is especially true insofar as iron fortification is concerned, and in recent years there have been a number of reports in which these problems have been discussed and guidelines for the planning and implementation of such programs have been laid down.[13,146,235,237] If effective dietary fortification is to be achieved, a series of steps must be followed (Table IX).

The initial iron nutrition of the population must be evaluated before embarking on any program of for-

TABLE IX
STEPS IN THE ACHIEVEMENT OF EFFECTIVE DIETARY IRON FORTIFICATION

1. Define the iron nutrition of the population.
2. Select a suitable iron compound.
3. Choose an appropriate vehicle
4. Establish the acceptability of the appearance, taste and shelf life of the fortified vehicle and of typical meals containing it.
5. Measure the absorption of iron from meals containing the fortified vehicle.
6. Check the effectiveness of the fortification by a field trial.
7. Monitor the iron nutrition after introduction.

tification. In this context it is particularly important to define the prevalence of iron deficiency in pregnant women, since it provides a useful guide to the overall state of iron nutrition in the population as a whole. If the prevalence is such as to warrant intervention, then more information must be obtained on the etiologic factors involved and on other deficiency states. In this context, a clear distinction can be made between industrialized countries on the one hand, and developing countries on the other. In the former, iron nutrition is closely correlated with the total caloric intake, since the iron content in mixed Western-type diets is very constant, being approximately 6mg/100kcal.[illegible] However, in developing countries particular attention must be directed towards non-physiologic iron losses, such as hookworm infestation, and towards the nature of the diet, since nutritional iron deficiency may be due to a low iron intake, to low bio-availability of the dietary iron, or to a combination of both factors.[illegible] If the iron deficiency is largely the result of hookworm infestation, then the expected effects of iron fortification may be partially vitiated by the fact that increased iron absorption and hence hemoglobin formation is paralleled by increased hemoglobin iron losses from the gut. If the problem is one of bio-availability, a distinction must be made between the intrinsic iron in the diet and extraneous contaminating iron, such as dirt. Some diets contain a lot of contaminating iron which is not absorbed, but the bio-availability of the remaining intrinsic iron may be quite good.[illegible] If this is the case, then fortification of the diet with iron could prove effective. On the other hand, if the intrinsic iron is poorly bio-available (e.g. a maize diet), then fortification with iron is unlikely to be effective, since the added iron will be as poorly absorbed as the intrinsic iron.[illegible] In such circumstances it may be more appropriate to attempt to improve the absorption of the intrinsic dietary iron, for example by increasing the intake of ascorbic acid. This has been shown to enhance the absorption of the intrinsic dietary iron as long as it is not destroyed during the preparation of the food. It will withstand boiling, but is oxidized and rendered ineffective by the higher temperatures of baking.[illegible] Ascorbic acid is, however, relatively expensive and current efforts are being directed towards finding effective but cheaper alternatives.

The choice of a suitable *iron compound* is of paramount importance, since there is good evidence that many of those used in the past, such as large particle reduced iron, ferric orthophosphate and ferric pyrophosphate are all poorly absorbed.[illegible] In assessing the suitability of any proposed compound it is helpful to measure its effectiveness against that of ferrous sulfate, which is highly bio-available. The methods by which this is done have varied.[illegible] While young chicks and rats have been widely used as animal models in testing the relative bio-availability of different iron compounds,[illegible] species differences and methodologic difficulties have bedevilled the interpretation of such data, and currently attention is being directed to *in vitro* tests aimed at measuring the relative solubility of a variety of iron compounds and of dietary iron in hydrochloric acid,[illegible] in pepsin-hydrochloric acid mixtures,[illegible] and in gastric juice.[illegible] However, the ultimate test of any compound is the direct measurement of its bio-availability in man when fed in representative diets consumed by the population concerned. The compounds that are currently used are listed in Table X.[illegible]

Current data suggest that the iron from most of these sources is relatively well absorbed. Former problems relating to the absorbability of iron powders have been largely overcome by reduction in

TABLE X
IRON FORTIFICANTS (INCLUDING RELATIVE COSTS*)

COMMONLY USED COMPOUNDS
- Ferrous sulfate (1.0)
- Iron powders
  - (a) reduced iron (2.3)
  - (b) electrolytic iron (4.5)
  - (c) carbonyl iron (4.9)
- Ferric orthophosphate (2.5)

LESS COMMONLY USED COMPOUNDS
- Ferrous fumarate (3.5)
- Ferrous gluconate (5.0)
- Sodium iron pyrophosphate (2.9)
- Ferrous citrate (11.0)
- Ferric glycerophosphate (17.6)

EXPERIMENTAL IRON COMPOUND
- Sodium ferric EDTA (4.2)

*The relative bio-availability of the iron compounds has been taken into consideration in assessing costs.

their particle size and surface area. For example, if the particle size of reduced iron is sufficiently small, it is absorbed as well as the iron in ferrous sulfate when baked into bread rolls.[23] It has also been shown that the relative absorption of iron in ferric orthophosphate is similarly affected by particle size.[24] However, there is evidence that it is not the particle size *per se* that is the major determinant of the amounts of a particular iron compound that are absorbed. The reactive surface area and the dissolution rate in hydrochloric acid are better predictors.[21] In choosing a particular compound there are other important considerations relating to possible reactions with either the vehicle to which it is added or other compounds of the diet. Thus high density iron powders may be difficult to distribute evenly in powdered foods, while metallic iron may be removed by magnets employed to remove metal contaminants during food processing.[25,26] On the other hand, more reactive compounds, such as ferrous sulfate, may be associated with a number of undesirable changes in food, including off-colors, -odors and -flavors. Of the more recently tested compounds, sodium iron-EDTA holds some promise. It has the advantages of being stable, of exchanging with non-heme food iron, and because it is less susceptible to inhibitory ligands in "poor" diets, more iron is actually absorbed from the non-heme iron pool present in the meal than if it is fortified with ferrous sulfate.[12,13,19,27,28,29,30]

The choice of a *vehicle* for the iron fortificant depends on a number of factors. It must obviously be a dietary constituent consumed by large sections of the population, and should ideally be manufactured at relatively few production centers, so that addition of the fortificant can be monitored. The most widely fortified food items in Western countries are cereals, and it has been estimated that 88mg reduced iron can be added per kg wheat flour without affecting its palatability and shelf life.[3] In the United Kingdom average flour consumption is about 1.5kg per person per week, but in the United States the figure is only about half as much.[32,33] Many infant foods and milk powders for infants are routinely fortified with various forms of iron. The bio-availability of such iron is strikingly improved when ascorbic acid is present (Fig. 30).[9,23,25,26] Beverages also represent potential vehicles for iron and have the advantage that the additive can, to some degree, be restricted to certain target groups, since they are generally consumed by identifiable segments of the population. In other countries special problems may arise because of the decentralization of food production, and because some of the major cereal staples do not lend themselves readily to iron fortification. For example, rice is often washed before cooking, and this may remove the added iron. Other possible vehicles are table salt and sugar. A practical problem with salt is its tendency to discolor when fortified with iron and or ascorbic acid.

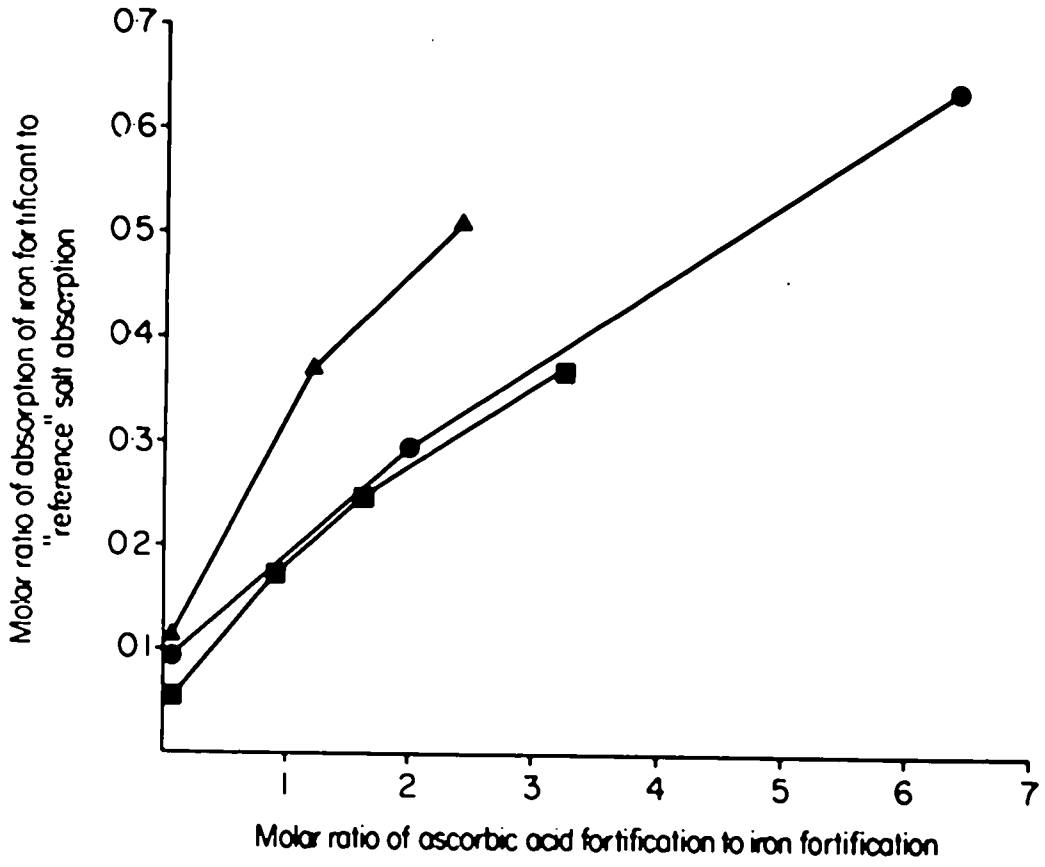

FIGURE 30

The improvement in the absorption of iron fortificants due to increasing the ratio of ascorbic acid to iron. The ratio of the amount of iron absorbed from the fortified foodstuff to the amount absorbed from a standard dose of ferrous ascorbate was used as a measure of iron absorption, since the ratio corrects results for individual variations in nutritional status. (Key to figure —● infant milk formula; ▲ infant cereal B, ■ infant cereal C). (After Derman and coworkers[93])

particularly in hot humid climates.[236,239,240] This is particularly so with coarse cooking salt. The problem can, however, be overcome, at least partially,[237,240] and two preliminary trials using salt fortified with iron have already been reported.[239,241] The fact that sugar may be added to tea or coffee restricts the choice of iron compounds, since black or blue colors result from the reaction of iron with tannins.[242] With coffee, iron-EDTA is not subject to this drawback. In Thailand a fish sauce was successfully fortified with the iron-EDTA, but its use varied greatly from one region to another.[243] Local dietary customs, including the use of condiments such as monosodium glutamate and curry powders, may offer opportunities for fortification, and all the possibilities should be examined before a decision is made. As mentioned earlier, the final choice will depend not only on the degree to which the added iron is absorbed, but also on the consumer acceptability of the fortified vehicle, including the appearance and taste of typical meals containing it and its shelf life. In addition to reactions with tannates and other phenolic compounds, a black discoloration may result from reactions with sulfur containing compounds, and various oxidative reactions may be catalyzed, with the development of unacceptable odors and flavors as well as colors.[156,320]

If a suitable compound and vehicle have been selected, it can be expected that the bio-availability of the added iron will be similar to that of the

non-heme food iron in the diet, since the added iron will enter the common pool. This must nevertheless be formally established, firstly by isotopic studies and then by a field trial using the population concerned.[22,23] The field trial will establish the adequacy of the distribution system, and whether the level of fortification is sufficient to counter the iron deficiency. After the introduction of the fortification, it is essential to carry out a long-term surveillance of iron nutrition in order to establish that the program is effective.

A final consideration with regard to any fortification program is the question of its *safety*. Thus follow-up monitoring programs must subserve a dual function. Not only must they be concerned with the segment of the population, including infants and women who are likely to benefit from iron fortification of the diet, but equal attention must be directed to the more replete adult male population in order to ensure that they do not accumulate excessive quantities of iron. Two groups are particularly at risk, namely subjects who have inherited the mutant gene responsible for the iron storage disease, idiopathic hemochromatosis, and patients with thalassemia.[32] The source of the iron in thalassemia major depends on the philosophy of treatment. In industrialized countries it is largely derived from blood transfusions, since the current policy is to maintain the hemoglobin concentration above 10g/dl.[33] When this is done, there is a marked reduction in iron absorption.[124] On the other hand, the gut is the major, if not the only source of iron in developing areas, since transfusion therapy is not applied. Under such circumstances, patients succumb at an early age and it is unlikely that iron fortification would modify the course of events significantly. At more risk are individuals, such as those with thalassemia intermedia and other thalassemic syndromes, who are less severely affected hematologically and yet absorb iron excessively.[125] For example, α-thalassemia occurs with a frequency of 20 to 30% in Thailand, while thalassemia is found in 3 to 9%, hemoglobin E in 13% and hemoglobin Constant Spring in at least 4% of the population.[125a] As a result, it has been estimated that there are 500,000 individuals in Thailand with major thalassemic syndromes, the most common being hemoglobin H disease and β-thalassemia/hemoglobin E disease. Subjects with both these syndromes have been shown to accumulate iron, with the more severe involvement occurring in β thalassemia/hemoglobin E disease (a mean plasma ferritin concentration of 2158 μg/l in 174 patients).[126a] These figures underline the difficulties that might arise in weighing the pros and cons of an iron fortification program in a country where iron deficiency is common but in which a significant proportion of the population carry iron-loading genes. The situation with regard to idiopathic hemochromatosis has been discussed in detail elsewhere.[32] In summary, from what is known of iron balance, it would be expected that increased fortification of the diet with iron in Western countries would lead to clinical manifestations occurring at an earlier age in subjects homozygous for the gene (Fig. 31). Stores in heterozygotes would also be greater, but equilibration of the body iron content would occur at a time well before the accumulation of massive stores. At the same time it must be accepted that this point remains conjectural, and careful monitoring of the storage iron concentrations is mandatory when the level of iron fortification is increased. Fortunately, the availability of methods for measuring the plasma ferritin concentration, which reflects the size of the body iron stores, provides a practical method for doing this. In addition, the recent demonstration that the heterozygous and homozygous relatives of diagnosed hemochromatotic patients can be identified by HL-A (Human Leukocyte-Locus A) typing provides a way of establishing what the consequences to each will be.[56,126b] These points are raised because a proposal to increase the enrichment of flour in the USA to 88mg/kg was eventually rejected on several grounds, one of which was its safety. The question of safety is based on the fact that any fortification program designed to satisfy the needs of a vulnerable segment of the population, such as women of childbearing age, exposes iron-replete males to iron intakes significantly greater than their modest requirements since their caloric intake, and hence iron intake, is greater than that of females.[19] Of interest in this regard is the fact that in Sweden the iron intake has for the last ten years been considerably higher than would have been achieved by the increased fortification proposed in the USA, but there is as yet no suggestion of any increase in the clinical incidence of idiopathic hemochromatosis in western Sweden.[133] While several cases of iron overload have been detected in northern Sweden,[133a] the relationship of this finding to the iron fortification program is not clear. On the positive side, it has been possible to show that there has been a striking decrease in the incidence of iron deficiency anemia in Swedish women over the same period. However, it is clear that iron fortification has not been the only factor responsible for this, since the increased taking of iron tablets, the increased use of contraceptive pills and a rise in the

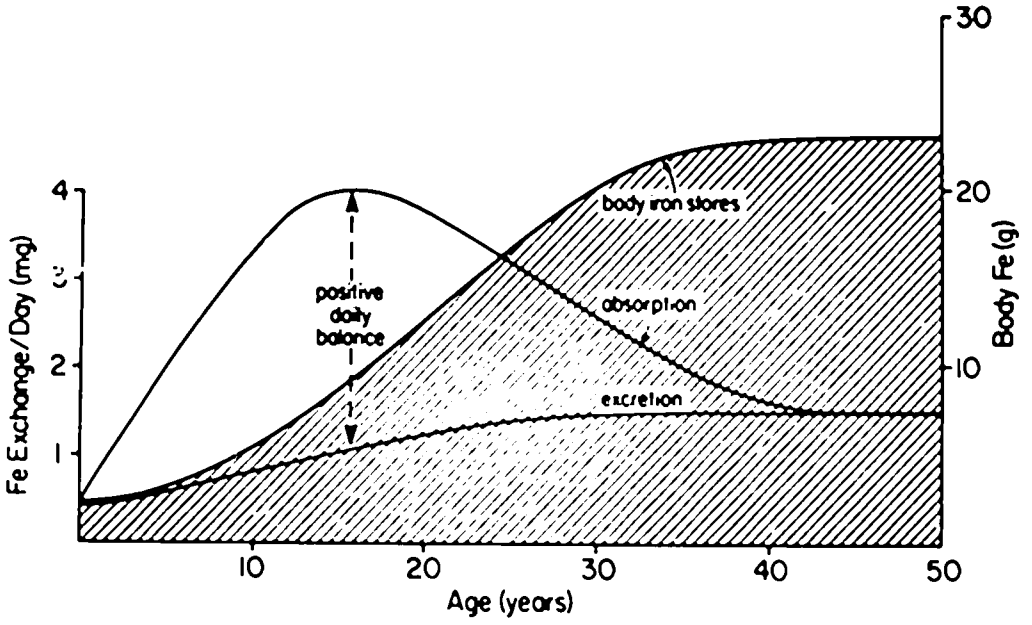

FIGURE 31

A schematic and idealized representation of how the body iron content increases over the years in idiopathic hemochromatosis. Note that the rate of iron absorption decreases as stores reach massive proportions, while the rate of iron excretion rises, but to a lesser extent. Eventually equilibration is reached, but by this time the body iron content is very large. Were the dietary intake to be fortified with iron, initial absorption rates would be expected to be higher and hence the final equilibration point would be reached at an earlier age. As a result, clinical manifestations would appear earlier. The same general principles probably hold for subjects heterozygous for the abnormal mutant gene, but since their stores are at best modestly raised on current Western-type diets, iron fortification would be expected to have a very limited effect, with some increase in iron stores, but not to levels anywhere near those encountered in homozygous individuals. (Data from Bothwell and coworkers,[29] and Bezwoda and coworkers[31])

consumption of ascorbic acid tablets have also contributed significantly (Fig. 32). These results underline the importance of recognizing the many variables which may affect the consequences of the introduction of an iron fortification program.

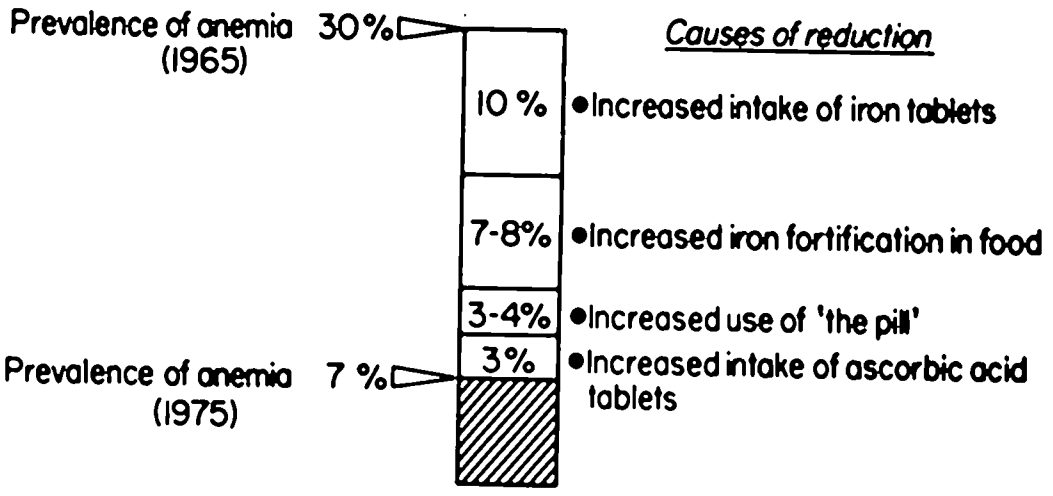

FIGURE 32

Causes of reduction in prevalence of anemia in Swedish women of fertile age. (After Hallberg and coworkers[133]).

VII.
Treatment of Iron Deficiency

The previous section was concerned with epidemiologic aspects of iron deficiency, both in terms of presentation and therapy. In this final section, attention will be directed to the principles of therapy in the individual patient. At the outset, it is essential to emphasize that the physician must establish why the patient has developed iron deficiency anemia, and if it is due to pathologic bleeding, the source of the blood loss must be identified and appropriate treatment instituted. In premenopausal women iron deficiency is usually nutritional in origin, although it must not be forgotten that pathologic hemorrhage can occur in this age group also. As was mentioned in a previous section, women are often unaware of the extent of their menstrual losses, and if there is any doubt, a method has been described for quantitating them.[146] Iron nutrition improves after the menopause, because of the removal of the menstrual drain. As a result, iron stores tend to rise in post-menopausal women,[22] even in communities where iron deficiency is common (Fig. 33).[210] It must therefore not be assumed that iron deficiency anemia in a post-menopausal woman is nutritional in origin. Instead, every attempt must be made to exclude a source of pathologic blood loss.

The Choice of Therapy: Having established the cause of the iron deficiency, and instituted appropriate treatment of the cause of any pathologic bleeding, the treatment of the iron deficiency can be undertaken. This has established itself as one of the most satisfying of therapeutic exercises. There are many effective and cheap preparations of iron for oral administration, and if there are no complicating features, such as infection or concomitant folate deficiency, there are only three reasons why their prescription might fail to correct the deficiency. By far the most likely is that the patient is not taking the medication, and this should be confirmed or eliminated without delay by careful questioning and by checking the number of remaining tablets at each visit. (If doubt still exists, it is possible to test for the presence of unabsorbed medicinal iron in the stool by using the Prussian Blue reaction[36]). The second possibility is that bleeding is continuing at a rate faster than the erythroid marrow can make good the losses. Hemorrhage of this degree can, however, be detected easily. The third and least likely explanation is that the iron is not being absorbed. If the bio-availability of the iron preparation is not in question, such malabsorption is nearly always due to idiopathic steatorrhea or tropical sprue.

Iron can also be administered by injection. The use of such preparations avoids the problem of poor patient compliance and the rare instances of malabsorption, but is no more effective in correcting the anemia than oral therapy, and is more expensive and less safe. As normal hemoglobin concentrations are approached, however, the absorption rate falls, and if replenishing the body iron reserve is desired in addition to correcting the anemia, oral treatment must be continued for several months longer. Administration of the iron parenterally makes it possible to replace the stores without delay but such therapy is expensive and is occasionally associated with potentially serious side effects. Other less important disadvantages of parenteral iron preparations are that they interfere with the laboratory measurement of the plasma iron concentration for several days, and with the assessment of the reticuloendothelial iron stores for many months. For these various reasons, treat-

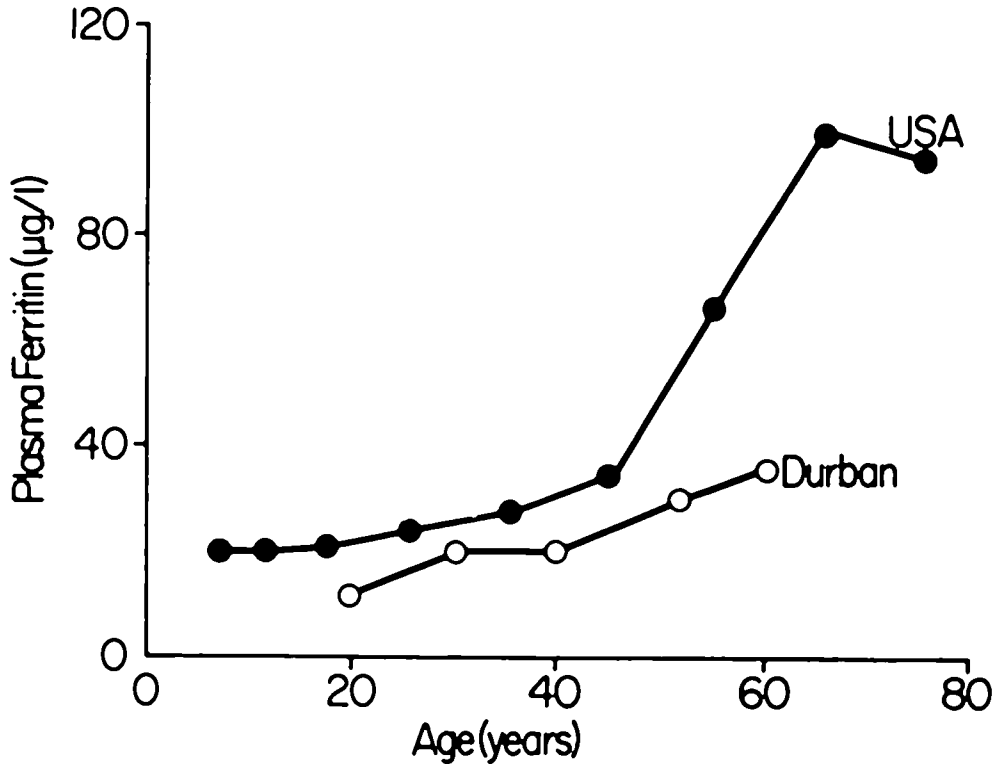

FIGURE 33

Median plasma ferritin concentrations in two groups of women, the one in the Northwestern USA and the other in Chatsworth, Durban. (Data from Cook and coworkers[73] and MacPhail and coworkers[111]).

ment should be with oral preparations in most patients, and it is only when malabsorption is present, or in those rare instances when oral iron cannot be tolerated, or in the totally unreliable patient, that parenteral iron should be administered. The potential for gastro-intestinal irritation may make oral therapy inadvisable for patients with regional ileitis, ulcerative colitis and peptic ulceration, although in fact most patients with these conditions tolerate it surprisingly well.

In rare instances iron deficiency anemia can be treated initially by blood transfusion. It is indicated when the severity of the anemia threatens life, and this is a question of the physician's judgment. Transfusion should never be undertaken without good reason, since it is not without hazard.

The Bone Marrow Response to Iron Deficiency: The ability of the erythroid marrow to increase the rate of synthesis of hemoglobin so as to make good the shortfall is dependent on the amount of iron available to the red cell precursors. This is a function of the plasma iron concentration: if it can be kept above 70 µg/dl throughout the 24 hours, erythropoiesis may increase fourfold, whereas if the amount absorbed is insufficient to achieve this, it will only double or treble.[134] The absorption of 40-50mg iron per day will permit a red cell production rate of about three times normal, and if there is no hemorrhage the hemoglobin concentration will rise at an average rate of about 0.2g/dl/day,[37] although figures somewhat less than this may occur if the anemia is very mild.

The Rate of Iron Absorption During Therapy: The rate of iron absorption is dependent on the severity of the anemia. Ten days after starting the treatment of a group of subjects with iron deficiency anemia, about 20% of the 100mg ferrous iron which was

being administered three times a day as ferrous sulfate was being absorbed.[128] The mean hemoglobin concentration at this stage was 9.5g/dl. After 30 days, when the hemoglobin concentration had risen to over 12g/dl, the absorption rate had fallen to 11% (Fig. 34). The amount of iron absorbed obviously depends also on the amount of iron ingested. If 74mg iron are administered three times a day, about 60% more iron is absorbed than if only half this dose is taken.[132] Another important variable is whether the iron preparation is taken in the fasting state or after meals. In one study the absorption of a 30mg dose taken when the stomach was empty was 40% greater than when it was taken after meals.[42] The degree to which absorption is inhibited by food depends upon the composition of the meal.[137] In one study absorption was reduced to only one-third or even less by a standard breakfast,[135] and in another, to less than one-fifth by a vegetable meal.[92] However, when a direct comparison was made between the absorption of a 100mg tablet of iron from different meals, more was absorbed from

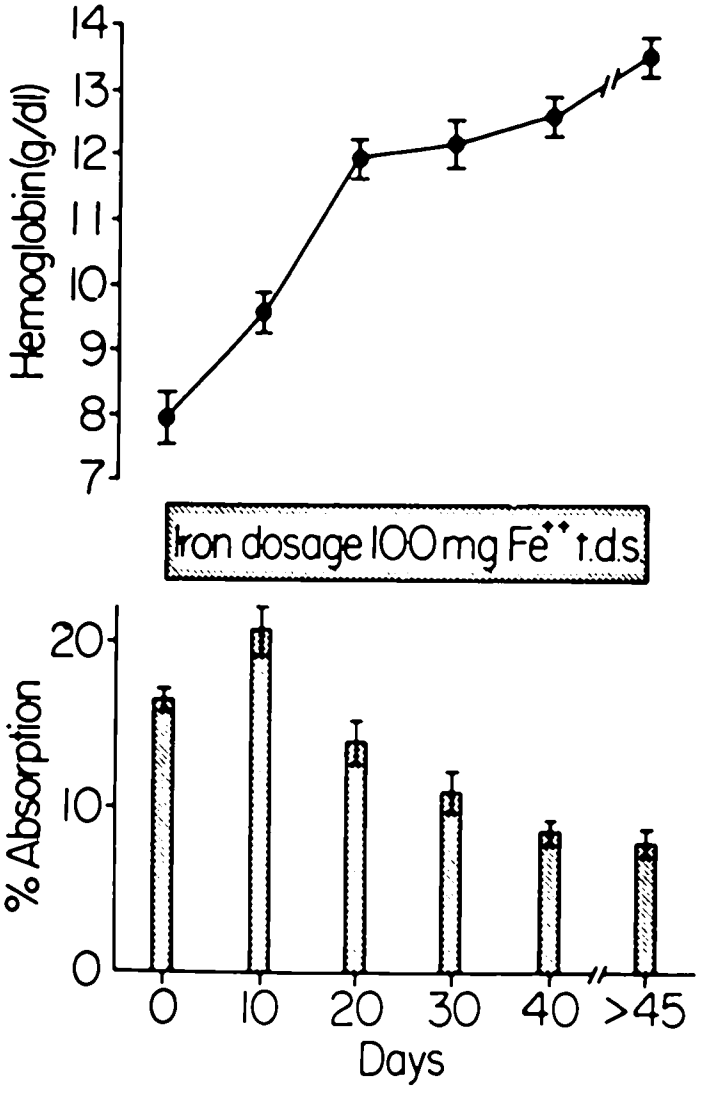

FIGURE 34

Iron absorption (mean ± S.E.) during continuous treatment in patients with iron deficiency anemia. The iron was given as ferrous sulfate in a dose of 100 mg three times daily with meals. (After Norrby and Sölvell[128]).

a rice meal than from one containing meat.[137] Because of the significant inhibition that food exerts on the absorption of therapeutic iron it is, in general, preferable to administer the iron in the fasting state, even though the dose may have to be reduced because of gastrointestinal side-effects. While food or antacids permit larger doses to be swallowed, absorption is correspondingly reduced and becomes much less predictable.

The nature of the oral iron preparation also determines the bio-availability of the iron, and therefore the amount that can be absorbed from a given dose. It has been well shown that the absorption is about three times greater at a dosage of 30mg iron if a ferrous salt is administered than if the iron is in the ferric state,[11] and with larger doses the difference is even more marked. The nature of the anion does not appear to matter greatly; ferrous sulfate, lactate, fumarate, glycine sulfate, glutamate and gluconate are absorbed to about the same degree, although there is evidence indicating that the succinate may be absorbed about 30% better (Fig. 35),[61,66,94,142,144] and that a similar enhancement is obtained if succinic acid is added to a ferrous salt.[68] The addition of ascorbic acid in sufficient quantity (200mg or more) increases absorption by at least 30%, probably both by preserving the reduced state of the iron and by forming soluble complexes with it.[11] This increased bio-availability results also in a significant increase in side-effects,[143,145] however, and since ascorbic acid is more expensive than ferrous sulfate, and its inclusion in the preparation achieves no more than could be achieved by in-

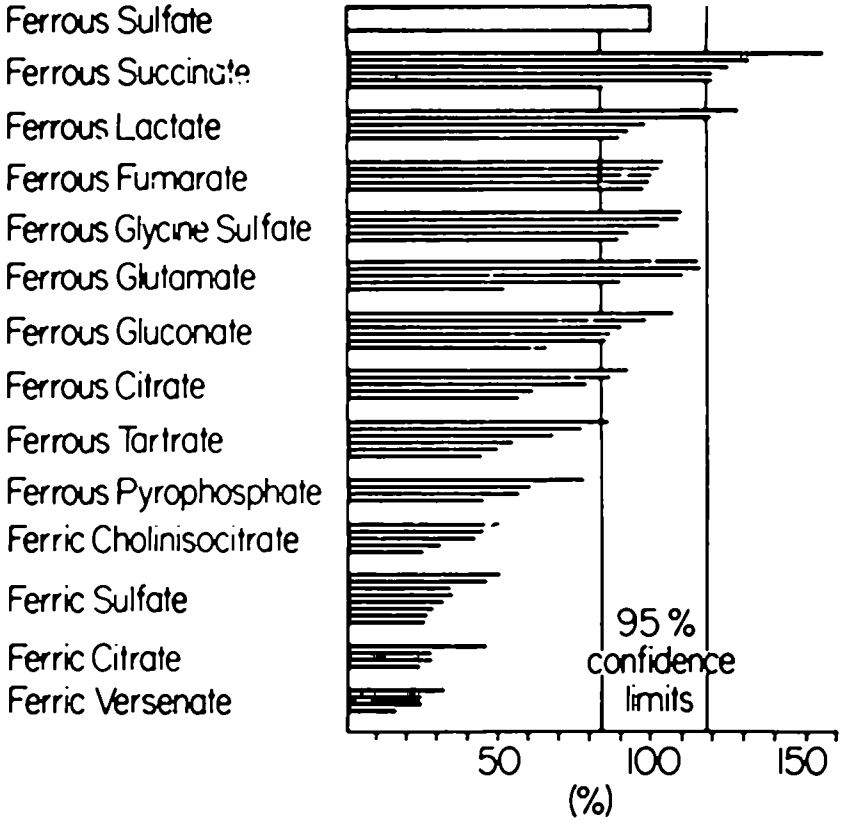

FIGURE 35

A comparison of the absorption rates with different iron salts. In these studies a daily dose of 30 mg iron as ferrous sulfate was alternated with another iron salt in similar dosage labelled with a second isotope over a period of 10 days. (Aiter Brise and Hallberg[94]).

creasing the dose of ferrous sulfate, its value is questionable. Some increase in absorption has also been achieved with very large doses of mannitol, sorbitol and D-xylose, but they produce unacceptable side-effects. Other carbohydrates, surface-active agents, inorganic salts, amino-acids and vitamins have also been tried, but without significant benefit.[43-45]

The Choice of an Oral Iron Compound: While the plethora of preparations on the market can easily confuse the physician, the choice is essentially a simple one. The 40-60mg iron which is required each day to permit a trebling of red cell production can easily be absorbed by subjects with hemoglobin concentrations of 10g dl or less from doses of between 36 and 74mg iron administered three times a day as a ferrous salt. Significantly more will be absorbed if a fourth dose is taken late at night.

Gastrointestinal side-effects represent the main limiting factor in oral iron therapy. A proportion of patients complain of nausea, epigastric discomfort and distention, heartburn, diarrhea or constipation. While there is no doubt that iron can produce dose-related nausea and epigastric pain, the evidence for the psychologic origin of the symptoms in some subjects is convincing. Fourteen of a group of sixteen patients who experienced symptoms while taking green ferrous sulfate tablets had none when white ferrous sulfate tablets were substituted.[174] In another study, lactose tablets labelled "Iron Pills" produced symptoms in the same percentage of subjects as did genuine iron pills labelled "Iron Pills", whereas identical lactose tablets labelled "Control Pills" did not.[181] It is equally clear that iron is not innocuous. In a double-blind Swedish study in which preparations of various ferrous salts containing approximately 200mg iron were compared with placebo tablets, twice as many subjects experienced side-effects with the iron,[143] and when the dose of iron was increased the percentage of subjects experiencing side-effects increased in proportion (Fig. 36). In fact, because compliance is so adversely affected by side-effects which are dose-related, a good case can be made for modifying the treatment strategy in subjects with only mild anemia. In such individuals a satisfactory though slow hematological response can be obtained with a single daily tablet containing 36 to 74 mg iron.

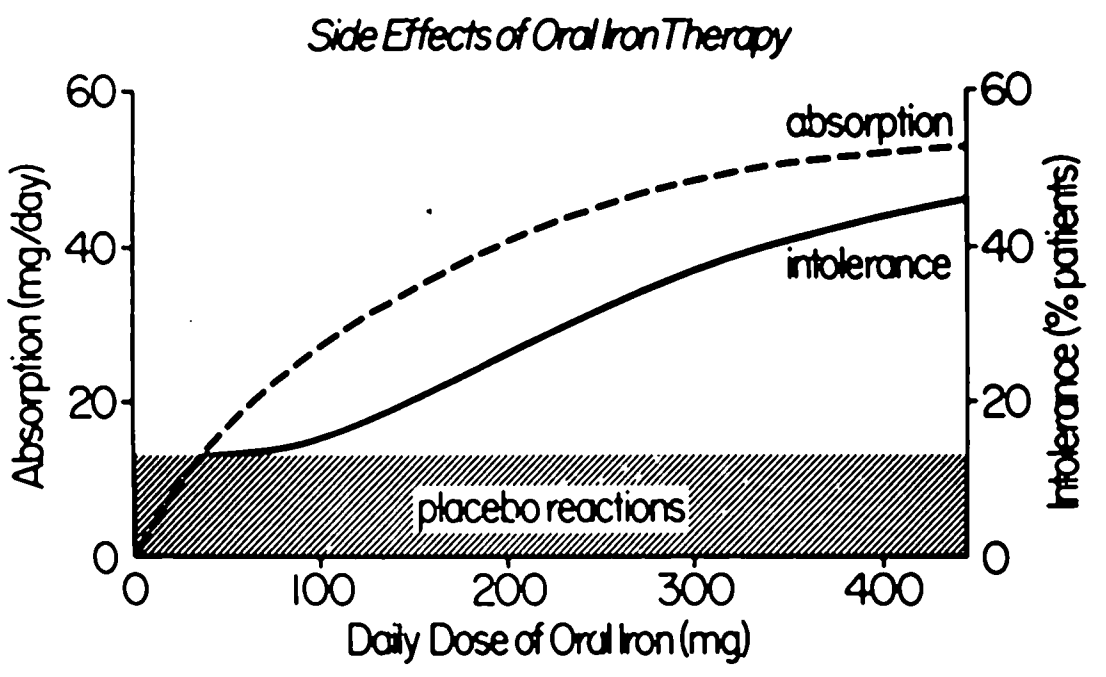

FIGURE 36

The rise in the prevalence of side-effects (solid line) with increasing absorption of therapeutic iron (dotted line). (Data from Sölvell, 1979).

Since the gastric irritation which leads to the nausea and epigastric pain is dose-related, and iron absorption occurs predominantly in the proximal duodenum, the designing of an iron preparation which will permit maximum absorption without gastric irritation has taxed the ingenuity of the pharmaceutical manufacturers. Over the years a number of slow-release preparations have been marketed, but trials of several of them have in the main indicated that absorption was not as high as that of preparations which dissolved promptly.[21,23,4,34,35] However, this is not true of all of them and good clinical responses have been also described.[33,136] In fact, there is evidence that the absorption of two of the currently available delayed-release preparations is the same as from ferrous sulfate when given in the fasting state, and somewhat better when given with food.[42,132,233] In addition, a reduced incidence of side-effects has been reported with one of them.[233] In the past such preparations have been much more expensive than conventional iron compounds but in some instances the price difference is now a good deal less.[32,174] On this basis, there may well be situations in which they offer special advantages. One such situation that was mentioned in an earlier section is the anemic pregnant woman who presents in the second half of pregnancy and who needs large doses of iron over a relatively short period to correct the anemia.[143] In general, however, the correction of iron deficiency does not require undue haste, and if the normal dosage of ordinary ferrous iron tablets produces symptoms, the dosage can be reduced.

While a preparation containing both iron and folate is useful for prophylaxis during pregnancy, combinations should be used for the treatment of anemia only when it is caused by deficiency of more than one nutrient. Indeed, this is the situation in pregnancy, since the supply of both iron and folate is frequently suboptimal. Although many preparations of iron contain other so-called hematinics, the use of such combinations deprives the physician of the confirmation of his diagnosis which might otherwise be gained from a specific therapeutic trial. A positive response to treatment can be defined as a daily increase in the hemoglobin concentration of more than 0.1 g/dl from the fourth day of treatment onwards.

Parenteral Iron Therapy. If oral iron is judged to be inappropriate for a particular patient, treatment with parenteral iron is equally effective. In one study of a large group of iron-deficient postpartum women, oral, intravenous and intramuscular therapy with iron produced average daily hemoglobin rises of 0.14, 0.15 and 0.13 g/dl respectively.[78] The results in several other studies have been similar.[207,240,276]

While a number of different parenteral preparations have been marketed at one time or another, iron-dextran is the one which has gained general acceptance. It consists of a complex of ferric hydroxide with dextrans of molecular weight between 5000 and 7000 daltons. It is presented as a colloidal solution containing 50 mg iron per ml, and may be injected either intramuscularly or intravenously. After intramuscular injection 50-90% of the iron is removed from the injection site within 4-5 days, but thereafter there is little further mobilization for up to 100 days.[122,139] The persistence of this iron within the muscle has given rise to concern when considered in conjunction with the reports of sarcomas in rats given massive intramuscular doses.[36,37,218] At least eight sarcomas have also been reported in association with its use in human subjects, but the significance of these findings, and the accuracy of the diagnosis in some cases, have recently been questioned.[37,38] Although the preparation was withdrawn from the market for a period, it has subsequently been re-introduced, and many millions of doses have been given. It would nevertheless seem preferable whenever possible to use the intravenous route rather than the intramuscular, when this is done, all the injected iron is taken up by the reticuloendothelial system. Additional disadvantages of the intramuscular route are pain at the injection site, and the skin may become stained for as long as two years. Other adverse reactions associated with the administration of iron-dextran include anaphylaxis, headache, malaise, fever, regional or general lymphadenopathy, arthralgia and urticaria,[21,235] and rheumatoid arthritis may be exacerbated.[241] It is, however, fair to point out that the therapeutic index is good. In one study of 2400 iron-deficient subjects, intravenous iron-dextran produced side effects in only 1-2%.[276]

If the preparation is administered intravenously it is particularly necessary to guard against the possibility of an anaphylactic reaction, and in the United States the standard policy is to give a small test dose initially and then wait for five minutes. Epinephrine, an injectable glucocorticosteroid and aminophylline must be at hand together with resuscitative equipment. If there is no reaction, 500 mg can then be given over a period of 5 to 10 minutes. This dose can be repeated at intervals of a

few days. Alternatively, the total amount can be administered over several hours diluted in normal saline to a concentration not exceeding 5%.[33] When this is done, the drip should be run in very slowly over the first few minutes because of the possibility of an anaphylactic response. The quantity of iron which should be injected can be calculated from the following formula:

$$\text{Total amount of iron required (mg)} = \frac{\text{hemoglobin deficit (g/dl)}}{100} \times \text{estimated blood volume} \times 3.4$$

This will provide enough iron to restore the hemoglobin concentration to normal, and if it is desired to recreate the body iron reserve, an additional 500 or 1000 mg may be given. The half-time of the iron dextran in the plasma is between 3 and 4 days,[314] but there is very little effect on the unsaturated iron-binding capacity, since virtually all of the iron remains attached to the dextran.[178] After having been taken up by the cells of the reticuloendothelial system, some of the iron becomes available for release to the plasma transferrin and transport to the bone marrow. During the month after administration only about 50% is utilized for hemoglobin synthesis,[309,310,314] and over the ensuing weeks the rate of blood formation gradually slows.[135] After three to five months 30% of the injected iron has still not been utilized;[233] virtually complete mobilization of the iron will occur eventually.[180] The reason for this restricted availability of iron-dextran is not clear. It can be seen within the reticuloendothelial cells after staining with potassium ferrocyanide, and the co-existence of iron deficiency anemia with apparently adequate iron stores can create diagnostic problems unless the possibility of delayed processing and release is appreciated.

VIII.
Summary

1. Iron deficiency is the most commonly recognized nutritional deficiency. It affects women more than men because their requirement for iron is greater and their iron intake less as a result of the lower food consumption.

2. The extra iron women need is to replace losses through menstruation and pregnancy. The median menstrual blood loss in Swedish and in British women adds 0.4-0.5 mg iron to the daily 0.7-0.8 mg lost by other routes. In as many as 10% of normal subjects, menstruation is the equivalent of more than 1 mg per day. Gestation diminishes the iron requirement during the first trimester because menstruation ceases, but during the second and third trimesters a total of about 5-6 mg per day is needed to supply the conceptus and for the expansion of the maternal red cell mass. A variable amount of blood is lost at delivery and in lochia during the puerperium, but this is partially offset by the recovery of the extra iron in maternal hemoglobin as the red cell mass returns to non-pregnant dimensions. The net iron cost of pregnancy is of the order of 500 mg.

3. Heme iron in food is absorbed well regardless of the composition of the diet. Non-heme food is generally less bio-available, and is susceptible to the action of a variety of promoters and inhibitors of absorption. Important promoters include meat, fish and ascorbic acid, and important iron inhibitors are tannins and bran. During digestion most of the non-heme iron enters a common intraluminal pool so that its bioavailability is determined by the various ligands present in the meal. The iron in staple foodstuffs such as wheat, rice and maize is poorly absorbed but the bio-availability is significantly improved if they are eaten with adequate quantities of meat, fish or ascorbic acid. These are relatively expensive, however, and the result is that the usual diet of much of the world's population, particularly in developing countries, provides too little absorbable iron for many women.

4. With adequate nutrition a reserve of iron is stored in the tissues in the form of ferritin and hemosiderin. This reserve is used to make good any shortfall, for example in pregnancy if, as is usually the case, enough iron cannot be obtained from the diet to expand the hemoglobin mass in addition to supplying the conceptus. The size of the body iron reserve is an index of the iron nutritional status. It can be most conveniently assessed by measuring the plasma ferritin concentration. A depleted or exhausted store indicates a state of iron deficiency. Once the iron deficiency is such as to compromise the supply to the bone marrow, the plasma transferrin concentration rises and the plasma iron concentration falls, so that the percentage transferrin saturation is decreased. In addition, the red cell free protoporphyrin concentration rises. Finally, the hemoglobin concentration falls. Because the range of hemoglobin concentrations in normal subjects is wide, mild anemia is difficult to detect unless the tests of the adequacy of the iron supply for erythropoiesis are performed in addition to measuring the hemoglobin concentration.

5. Severe anemia during pregnancy increases maternal mortality. Iron deficiency limits work capacity, and this is due to a skeletal muscle enzyme deficiency resulting in dysfunction as well as to the inadequate oxygen supply caused by the hemoglobin deficiency. Biochemical lesions in other tissues

have also been documented, but their clinical significance is less well established.

6. Iron deficiency can be prevented by providing the vulnerable members of the population with supplemental iron, or by fortifying the diet so that the iron nutrition of the whole population is improved. Antenatal clinics provide a good opportunity for supplementation. The dose required depends firstly on whether the iron preparation is to be given with meals when less is absorbed, or fasting when compliance is erratic, secondly, on the subject's iron nutritional status, and thirdly, on the stage of gestation. Dietary fortification ensures that all the individuals at risk are reached, but increases unnecessarily the iron intake of those who are iron-replete, especially those genetically susceptible to iron overload. If this approach is adopted, it is essential to monitor the iron nutrition of the various sectors of the population to ensure the safety of such individuals as well as to assess progress in eliminating iron deficiency. For a fortification program to succeed, a suitable vehicle must be found. It should be a dietary ingredient which is consumed by the whole population, is distributed from a few central points, and is not altered in shelf life, taste and appearance by the fortificant. The added iron must obviously be both cheap and adequately absorbed; since it is likely to enter the common pool of dietary non-heme iron during ingestation and be subject to the same inhibitory ligands, fortification with a promoter of iron absorption such as ascorbic acid may be indicated in certain circumstances.

IX.
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Guidelines for the Eradication of Iron Deficiency Anemia
Iron Deficiency in Infancy and Childhood

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