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IRON DEFICIENCY

MEDICAL GRAND ROUNDS
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The first description of what medical historians believe was iron deficiency anemia appeared in the "Papyrus Ebers", an Egyptian medical manual, in about 1500 B. C. In the sixteenth century, the malady known as chlorosis or "green sickness" was recognized and by the next century French physicians appreciated that iron salts were one part of effective therapy. Sydenham is credited with recognizing the specific importance of iron in this disorder. During the present century, volumes of data have been compiled which have documented the physiologic function of iron, the means by which iron balance is maintained and the causes, effects and therapeutic approach to the clinical disorder associated with body iron depletion. Despite the prevalence of this disease state (at least 18,000,000 cases are believed to exist at any one time in the U.S. alone) and the order with which numerous iron containing medications are administered, the general knowledge of physicians regarding the etiology, manifestations, diagnosis and management of iron deficiency is replete with misconceptions.

This discussion will attempt to deal with selected aspects of the problem of diminished body iron and to place the clinical approach to the condition in practical perspective.

The following points will be dealt with:

1. Definitions of the stages of iron deficiency
2. Mechanisms of maintenance of total body iron balance
3. Effects of diminished total body iron
4. Detection of iron deficiency
5. Causes of iron deficiency
6. Repletion of the iron deficient state
7. Prophylaxis of iron deficiency

Definitions:

The hypochromic, microcytic anemia that is a consequence of severe iron deficiency is usually a readily detected and simply diagnosed condition. This entity is present in less than 50% of persons with physiologically significant reductions in total body iron however. To emphasize that prior to this point:

a) physiologic mechanisms to restore body iron content are activated and
b) pathologic effects of iron store reduction take place

Finch has appropriately introduced terms to define these observations (24).

A. Iron depletion: The point at which enhancement of iron absorption is activated as a result of diminution of iron stores - approximately 400 - 500 mgm of storage iron.

B. Iron deficiency erythropoiesis: The point at which potential or actual impairment of erythropoiesis occurs due to diminished availability of iron for red cell production. Usually correlated with plasma iron levels.

C. Iron deficiency anemia: The point at which microcytic or hypochromic microcytic erythrocytes are produced by the erythron.

The ensuing discussion will review the data upon which these definitions are based and attempt to demonstrate how they can be clinically recognized and corrected.

The Maintenance of Iron Balance

Table 1 demonstrates the average values and distribution of Fe content of the normal adult male. (1, 2) The values for storage Fe vary considerably from these in pre-menopausal females and will be dealt with subsequently. Two to three grams are present in circulating erythrocyte hemoglobin and the next largest quantity is present in storage forms.

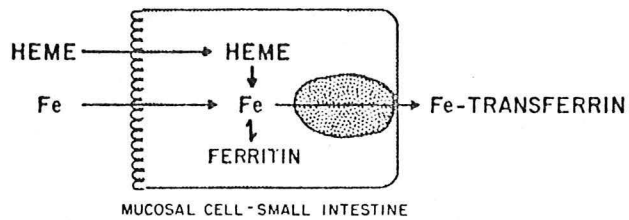
Compound	*Total in body (Gm)*	*Iron factor (Gm/Gm)*	*Total iron in compound (Gm)*	*Per cent of total body iron*	*Function*
Hemoglobin					
Peripheral blood	650.0	0.0034	2.21	64.0	O_2 transport
Bone marrow	25.0	0.0034	0.09	2.5	O_2 transport
Myoglobin	40.0	0.0034	0.14	4.0	O_2 transport and "storage"
Parenchymal or cellular					
Cytochrome	0.8	0.0043	0.0034	0.097	O_2 utilization
Catalase	5.0	0.009	0.0045	0.13	H_2O_2 destruction
Peroxidases	—	—	—	—	H_2O_2 destruction
Storage iron					
Ferritin	2.0	0.23	0.46	13.0	Fe storage
Hemosiderin	1.5	0.37	0.56	16.0	Fe storage
Transport iron	6.5	0.0004 to 0.0012	0.004	0.12	Fe transport
Total iron			3.47		

Table 1. Ref. 1.

Significant pathologic consequences occur as a result of excessive body iron - as discussed at these grand rounds last year (3) - and also from depletion of total body iron as being discussed presently. Thus the prevention of significant variations of body Fe content is an important physiologic function.

The maintenance of Fe homeostasis is a rather unique process since there is a major limitation to the excretion of Fe. (4, 5) The latter process occurs primarily through the sloughing of gastrointestinal mucosal cells and daily obligatory G.I. blood loss and can be maximally increased to only 2-4 mgm per day when iron overload exists. Thus balance is primarily maintained by altering the rate of absorption of Fe across the gastrointestinal mucosal surface. Numerous factors play a role in the final quantity of orally obtained iron which will be absorbed into the body as depicted in figure 1.

LUMINAL MUCOSAL CORPOREAL



DIETARY IRON:
- Quantity
- Chemical Form
- Physical Form

CHELATION & PRECIPITATION:
- Dietary Composition
- Intestinal Secretions

INTESTINAL MOTILITY

ANATOMY & HISTOLOGY:
- Absorptive Surface Area
- Defective Epithelial Cells
- Blood Flow
- Mucosal Lifespan

MUCOSAL IRON CONTENT:
- Quantity
- Chemical Form

BODY IRON STORES

IRON TURNOVER:
- Erythropoiesis
- Sideroblastic Disorders
- Anabolism - Catabolism
- Reticuloendothelial Block

HYPOXIA

IDIOPATHIC HEMOCHROMATOSIS

Fig. 1. Ref. 25

Luminal factors are generally of a secondary nature and are unlikely in themselves to be capable of maintaining normal balance. (6) The primary site of regulation is at the small intestinal mucosal cell which in turn alters rates of Fe absorption in response to alteration of body Fe content and rates of erythropoietic activity in the bone marrow. (7, 8)

Several features of the mucosal Fe absorption process have been well delineated and others are less clearly understood.

1. Mucosal Fe absorption is a two step process involving the initial uptake of a quantity of Fe from the lumen and the subsequent transfer of a varying proportion of that Fe to the carcass. (9, 10) The iron not transferred is stored in the cell, primarily as ferritin, and subsequently lost as the cell is normally sloughed.

2. Carcass Fe absorption is normally limited, since a balance is maintained between gain and loss - approximately 1-2 mgm per day.

3. Carcass Fe absorption has many features suggesting a specific facilitated or active transport process including rate limitation by increasing doses of iron, competitive inhibition by other heavy metals such as cobalt and manganese, and localization of the control site to the duodenum and proximal jejunum. (10-14)

4. Carcass Fe absorption is altered by certain physiologic derangements, particularly major enhancement occurs in the presence of Fe depletion and increased marrow erythroid activity. (4, 5) To a much lesser extent, iron overload and diminished erythropoiesis are associated with a decrease in absorption rates.

5. The uptake step into the mucosal cell does not appear to be the rate limiting transport site since it demonstrates no localization, linear dependence on dose, no competitive inhibition, a low temperature coefficient and is not enhanced with FeD or increased erythropoiesis. Uptake appears to depend only on the quantity and complexed form of the iron exposed to the luminal surface of the cell. (15)

6. Heme Fe is taken up by the cell as the heme molecule, the Fe then released by the heme oxygenase system and the Fe then enters into the usual absorption sequence. (16)

7. The site of the rate controlling step is most likely the basal membrane. The role of cell iron content and the mechanism of regulation by Fe stores and erythropoiesis remain unknown. (10, 11, 17) Specific intracellular carrier molecules have been proposed to contribute to this control (18, 19), but there is considerable evidence against this concept. (20-23)

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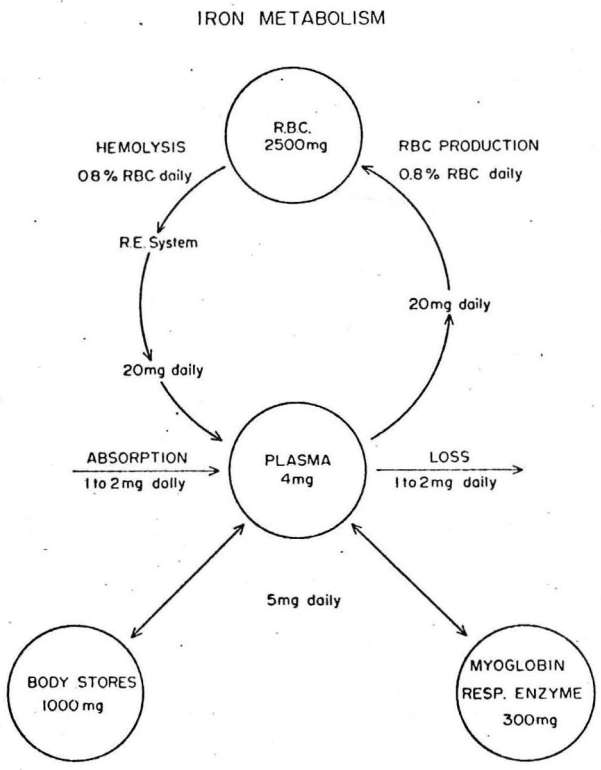
The Effects of Iron Deficiency:

To better understand the effects of reduced body iron content, a basic understanding of the general aspects of iron metabolism is necessary. Figure 2 depicts the major points of the distribution and turnover of iron in the normal steady state. (25)



The total body iron in the adult human is about 4 g and this quantity is maintained by a balance between absorption and body losses. Although the body absorbs only 1 to 2 mg daily to maintain equilibrium, the internal requirement for iron is much greater. A red blood cell has a normal lifespan of 120 days so that 0·8% of circulating erythrocytes are destroyed and replaced each day. A human with a 5 litre blood volume has about 2·5 g of iron incorporated into hemoglobin with a turnover of 20 mg of iron for hemoglobin degradation and production of an additional 5 mg of iron for other metabolic requirements. Most of this iron passes through the plasma for utilization. Disordered red blood cell metabolism or hemorrhage can cause marked changes in iron kinetics and metabolism because of the large percentage of body iron in circulating red blood cells.

Fig 2. Ref. 25

1. Circulating RBC contain 2500 mgm of Fe as hemoglobin. The normal RBC lifespan is approximately 120 days and thus 1/120 or 0.8% of this pool is renewed daily by the erythroid marrow. This results in the utilization of approximately 20 mgm of Fe for hemoglobin synthesis and the release of a like amount from hemoglobin degradation by the heme oxygenase system in reticulo-endothelial cells. (26)

2. The plasma iron pool consists primarily of transferrin bound iron and contains approximately 4 mgm of iron. Essentially all iron exchange between pools is mediated via the plasma compartment.(27) Thus to supply the iron necessary for erythropoiesis (20 mgm), myoglobin and respiratory enzyme synthesis (5 mgm) and to transport newly absorbed iron (1-2 mgm) this pool must turnover at least 6 times daily. (Due in part to incomplete or ineffective utilization of iron supply by these compartments, and to other less well understood modulations, the actual plasma turnover is 7-8 times per day). Thus significant perturbations in the normal requirements of or release by the non-plasma compartments would be expected to be readily reflected in the size or turnover of the plasma pool.

Certain features of transferrin are of importance to this discussion. It has a molecular weight of approximately 80,000 daltons and is synthesized primarily by hepatic parenchymal cells. (28) It consists of a single polypeptide chain having two potential binding sites for Fe. It now appears that these two binding sites, although having similar thermodynamic binding constants, are physiologically different in their capacity to deliver iron to the immature erythroid cell. (29-33) Nucleated red cells and reticulocytes have specific binding sites for transferrin but uptake of iron by these cells is more efficient from a fully saturated transferrin molecule than from a half saturated one. Transferrin synthesis is impaired in the presence of protein depletion and catabolism may be enhanced in the presence of inflammation and perhaps other protein catabolic states such as malignancy. (28, 34) The similarity to certain features of albumin metabolism is apparent.

Iron is also found in plasma as ferritin in a concentration approximately 1/50 of the total transferrin bound iron. (35) Recent data, however, has suggested that serum ferritin may reflect, even more sensitively, certain aspects of iron balance than transferrin bound iron.(36) In addition speculation now exists regarding a physiologic role for this second plasma iron pool. (37)

3. Storage Iron is found in both parenchymal cells and the reticuloendothelial cells of many organs. The major storage forms are ferritin and a denaturation product - hemosiderin. (39) The apoferritin molecule has a molecular weight of 450,000 daltons and is comprised of 24 identical protein subunits. The iron is found as an inorganic micelle in the center of the spherical apo-protein and contributes up to 25% of the total weight of the molecule when fully saturated. Iron is ultimately available for utilization from both of these storage forms. Ferritin synthesis occurs in most cells studied and is induced by the presence of iron. (40) The liver is the major storage organ containing approximately 500 mgm in parenchymal cells. These storage forms of iron, however, are not immediately available for utilization and the major source of iron for hemoglobin synthesis is the so called "labile iron pool" which is primarily the iron supplied from the daily degradation of senescent red cell hemoglobin which is then reutilized preferentially for new hemoglobin synthesis, after transport via the plasma transferrin pool. (27)

Iron Depletion:

Absolute quantitation of storage iron available for hemoglobin synthesis can be achieved by repeated phlebotomy until iron deficiency erythropoiesis is achieved. (41) Studies of this type indicate that the average adult male has 800-1000 mgm of storage iron. Otherwise apparently healthy, nulliparous menstruating females without a history of blood loss have stores averaging ~1/3 of this value. (41-44) In the face of normal red cell values, and normal serum iron and percent saturation of iron binding capacity, the values of storage iron can be at least as low as 60 mgm however. (42) The first demonstrable alteration in iron metabolism that occurs with progressive diminution of iron stores is an increase in iron absorption rates. (24, 45, 46) Definitive studies of the level of iron stores at which this physiological adaptation occurs are not available, but reasonable estimates suggest that below 400-500 mgm of storage iron enhancement may be measurable. Since this technique requires elaborate instrumentation, other methods for estimating iron stores at the stage of iron depletion have been sought. Table 2 lists several parameters of iron metabolism which have been investigated in this context.

Table 2. Laboratory Parameters in Iron Depletion

Method	Observed Values	Sensitivity	Ref.
Iron Absorption	Increased below 400 mg.	~~IIII~~	46
Serum Iron	Normal ($\geq$ 50mgm%)	0	24
% Saturation TIBC	$>$ 16%	0	24
Stainable marrow iron	0 - Trace below 150 mgm	~~III~~	43, 46-48
Chemical iron content	Decreased in $<$ 50%	~~II~~	38,49
Chelatable iron	Normal $\geq$ 75%	+	38,44,50-52
Serum Ferritin	?Normal	?0	35,56-59

Stainable marrow iron is presently the most proven parameter of diminished iron stores which is readily applicable to the clinical setting. Prussian Blue staining of marrow aspirated squash preparation reveals the presence primarily of hemosiderin in reticuloendothelial cells as well as non-heme iron granules in erythroblasts (sideroblasts). (43, 46-48)

Scott and Pritchard (43) found that 0-trace stainable iron was always associated with less than 150 mgm of mobilizable iron stores. (Fig 3) 1+ iron stores indicated less than 400 mgm of mobilizable iron. Consistent with this data was the finding by Heinrich (46) that iron absorption was always increased when stainable iron was absent or only trace in RE cells. (fig 4) He found that iron absorption might or might not be increased when stainable iron was 1+ but was never increased when 2+. (54) Thus one can assume that major body iron deficit is present when absent or trace iron is found on marrow iron stains. With slightly more iron present histologically, a major deficit may or may not be present. Two major sources of error can clinically alter this association:

1) If a patient has had previous parenteral iron therapy, stainable iron may be present in the marrow RE cells when body iron deficit is present because a portion is never available for hemoglobin synthesis. (55)

2) The superimposition of another mechanism of anemia upon iron store depletion will result in the deposition of the iron from the reduced hemoglobin mass into the RE cells. This will amount to approximately 150 mgm per each 1 gm/d l reduction in the circulating hemoglobin value and thus only a 3-4 gm/dl Hgb reduction may give normal appearing iron stores by stain.

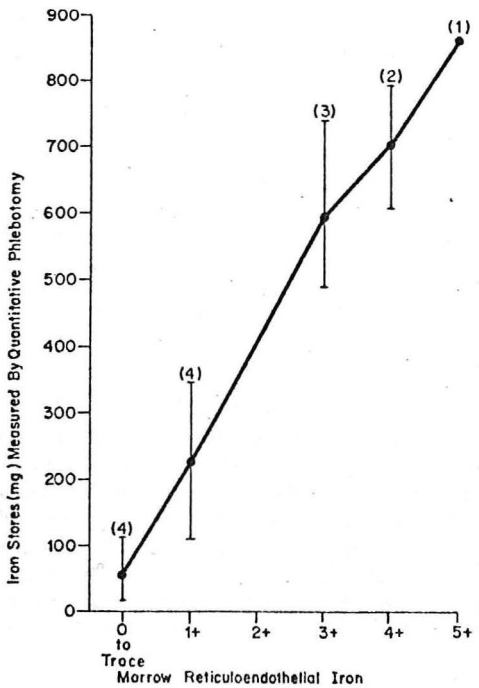
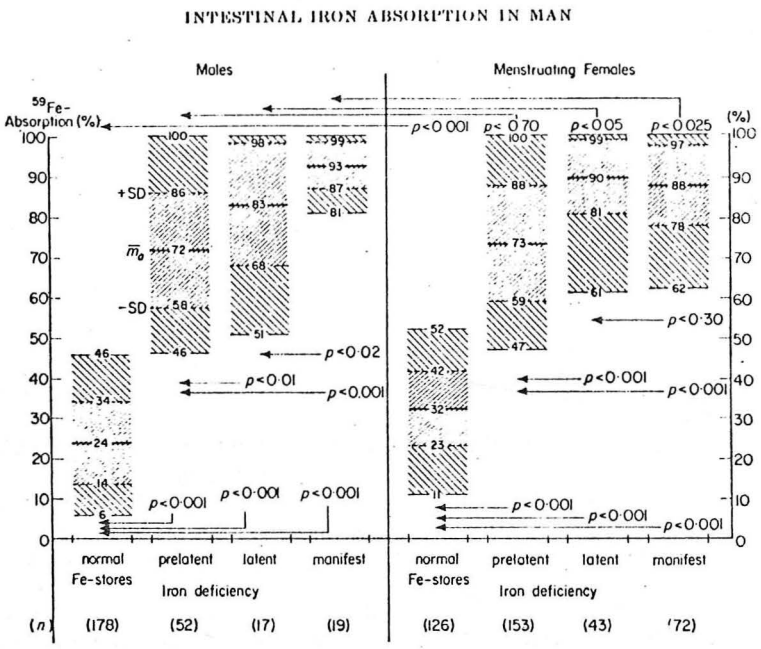


Fig 3. Ref. 43

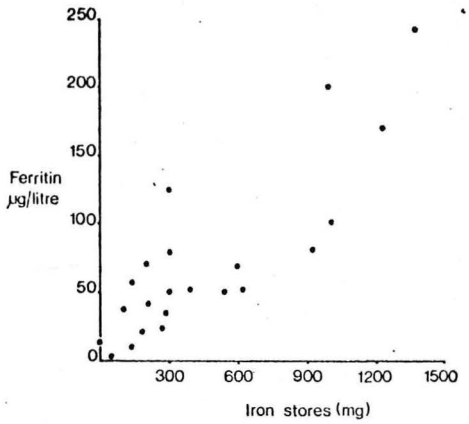


Intestinal ^{59}Fe-absorption (range and $\bar{m}_a \pm$ SD) from 0·56 mg $^{59}Fe^{2+}$ test dose in males and menstruating females with normal iron stores and prelatent, latent and manifest iron deficiency.

Fig 4. Ref. 45

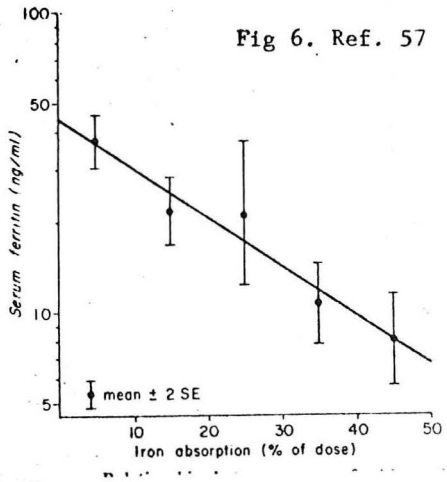
Serum Ferritin - the most recent advance in the attempt to develop more reliable yet less invasive techniques for the assessment of body iron status has been to evaluate the levels of ferritin in serum in normal individuals and a number of disease states. (35) Although good data exists relative to serum ferritin and the overt iron deficiency anemia state, (see below), insufficient studies are available to unequivocally state the role of this method in evaluating the iron depletion stage. In normal individuals there is a good correlation between iron stores guaged by phlebotomy and serum ferritin levels (56) fig (5). and also between iron absorption and serum ferritin.(57) fig (6).

Fig 5. Ref. 56



Iron stores and serum ferritin concentration.

Fig 6. Ref. 57



It would appear, however, that serum ferritin may be normal until iron stores are reduced below 100 mgm (58) and may also be normal when stainable iron is not present on histological stains (59). Thus, with the available data, it would appear that the simple measurement of serum ferritin will not detect the earliest stage of iron deficiency in a large number of patients.

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Iron Deficiency Erythropoiesis

The first pathological consequence of progressive depletion of iron stores that can be identified is the limitation of actual or potential erythropoiesis. Iron supply to the erythroid marrow is a function of iron stores, source of newly catabolized iron and the level of anemia. Crosby demonstrated that in the presence of hemolysis (60), or during phlebotomy of a patient with hemochromatosis (61), red cell production rates could achieve a six fold increase. Red cell production can be accurately quantitated by measuring plasma iron turnover and reticulocyte production indices. (62) In their classical studies, Hillman and Henderson documented the dependence of maximal red cell production on iron supply. (63) During phlebotomy with normal iron stores, red cell production increases as a response to the blood loss by a factor of 2-3.5 times at a hematocrit of 32-37%. When the rate of blood loss (degree of anemia) is greater (Hct. 25-30%) the production rate was similar unless sources of iron other than standard stores are available. Thus at these Hct levels oral iron supplements increased the rate to 4-5x, excess parenchymal cell iron to 5x, concomitant I.V. iron to 4.5-5.5x and non-viable red cells (newly catabolic iron) to 6-8x. It was of interest that in the face of depleted iron stores, oral iron supplements could support a 3-4x increase of red cell production rates. (Fig.7)

In contrast, patients with iron deficiency cannot increase the red cell production rate above normal and if the deficiency is severe enough, the rate may be decreased. (64, 65) Hillman and Henderson correlated the rate of red cell production with the serum iron level. (Fig 8). An even better parameter of limitation of iron supply to the erythroid marrow is the percent saturation of the total iron binding capacity - when this falls below 16%, iron deficient erythropoiesis is invariably present. (47, 62-64) Almost certainly, these observations relate to the ability of fully saturated transferrin molecules to deliver iron more efficiently to erythroblasts. (28-34). As serum iron falls, a larger percentage of transferrin molecules are half-saturated or do not contain iron at all, but are still able to compete for the binding sites on the erythroblast. Thus, the level of anemia, through the logarithmic increase of erythropoietic stimulation that occurs,(67) a normally functioning and potentially expandable erythron, the absence of other nutritional

FACTORS AFFECTING HEMOGLOBIN REGENERATION

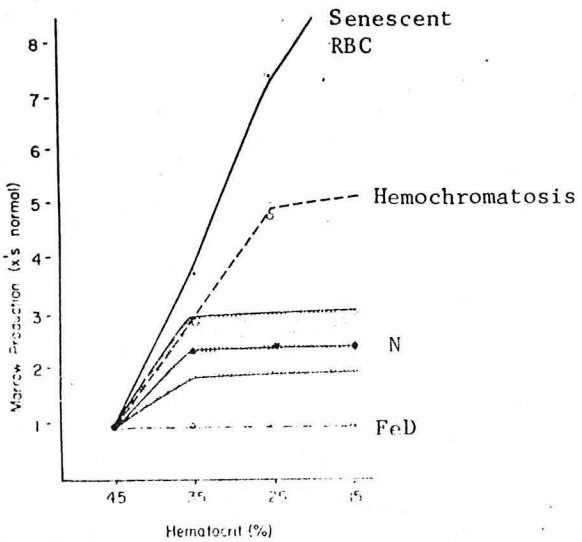
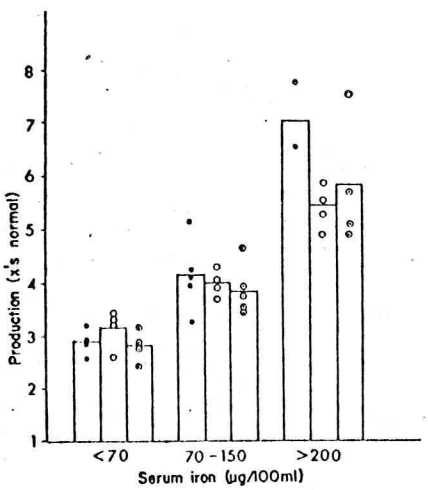


Fig 7. Ref. 66



.Fig 8. Ref. 63

or cofactor deficiencies (e.g. folic acid or B12) and iron supply all govern the absolute rate at which red cell production proceeds. It is of importance to emphasize that iron deficiency erythropoiesis can exist and yet the erythrocytes produced are normochromic, normocytic.(47, 63) Probably 50% of patients with this stage of iron deficiency have normal red cell indices. (24) The various parameters which are utilized for diagnosing total body iron store deficiency are listed in Table 3. Iron deficient erythropoiesis will

Table 3 Parameters of Iron Stores in Iron Deficiency Erythropoiesis

Method	Abnormal Values	Sensitivity	Specificity*	Ref.
Iron Absorption	Increased	~~++++~~	~~+++~~	46
Serum Iron	Decreased (< 70 µgs%)	~~++++~~	0	47,62-64
TIBC	Increased	~~++~~	~~+++~~	47,62-64
%TIBC Saturation	Decreased (<16%)	~~++++~~	0	47,62-64
Stainable Iron	0-Trace	~~++++~~	~~++++~~	43,46-48
Chemical Iron Content	Decreased	?	~~++++~~	38,49
Red Cell Protoporphyrin	Increased	~~++~~	0	68-71
Red Cell Indices	Normal	-	-	Definition
Serum Ferritin	?Decreased	?	~~++++~~	35,56-59,80,81

* Specificity in delineating iron store depletion as the cause of hypoferremia

occur in any state in which iron supply to the marrow is limited i.e. any hypoferremic state. The logical question, therefore, to ask is hypoferremia or a saturation of the TIBC of <16% specific for total body iron depletion? The answer is NO! Table 4 lists the causes of decreased serum iron or decreased % saturation of the TIBC.

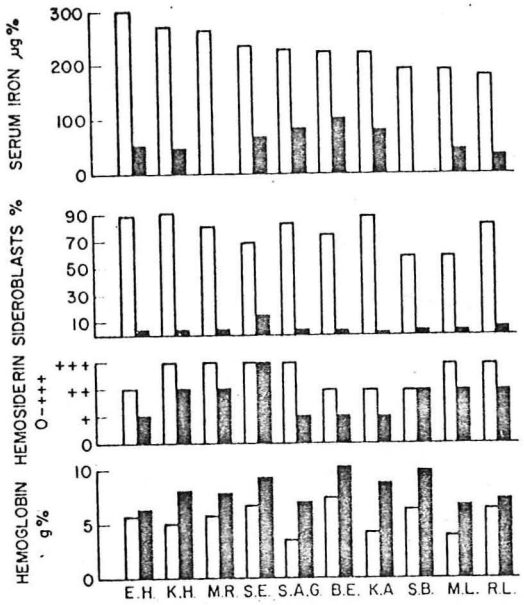
Table 4

CAUSES OF HYPOFERREMIA (SIDEROPENIA)

1. Fe deficiency (body iron depletion)
2. Anemia of Chronic Disease
3. Imbalance of Erythropoiesis and Senescence

The serum iron measurement has inherent problems with the major sources of error being iron contamination and thus values that are low are dependable. One exception is that a diurnal variation of plasma iron levels occurs with the lowest point being late afternoon or evening. (72) Slightly decreased levels at that time may not represent true iron deficiency.

Imbalance of erythropoiesis and senescence is a rather transient but not uncommon cause of temporary decrease in iron supply. Prior to equilibration of requirements and mobilization of stores, a sudden increase in erythropoiesis may be associated with a fall in the serum iron. This can be seen with acute blood loss (73) or the treatment of an underlying anemia with the appropriate measures, e.g. folic acid, B12 etc. (74) (Fig 9)



Megaloblastic anemia; white columns before and black columns after administration of specific therapy. From Weinfeld and Hansen[53].

Fig 9. Ref. 74

The major differential diagnostic dilemma is to separate the disordered iron kinetics of chronic disease (ACD) from the iron deficient state. The former is characterized by a mild hemolytic component, an inability to respond with adequate erythropoiesis and a defect in the reutilization of iron from senescent erythrocytes in some patients with infection, inflammation or malignancy.(75-79) The defective iron reutilization causes an impairment of iron supply and thus iron deficient erythropoiesis accompanied by hypoferremia and decreased saturation of the TIBC. Table 5 summarizes the data compiled by Bainton and Finch on the study of these states by the usual parameters of iron balance.

It is clear that in a given patient, the SI, TIBC and % saturation do not serve to differentiate the anemia of chronic disease from these two stages of iron deficiency. In those patients whose red cell indices were normal in the anemia of chronic disease, several did have values for % sat which exceeded 20%. In these patients Fe deficient erythropoiesis can be excuded but not iron depletion.

It is also of interest to note that the iron binding capacity may not be increased in 1/3 - 1/2 of patients with iron deficiency erythropoiesis or iron deficiency anemia. These patients had evidence of defects in albumin metabolism as well (serum albumin < 3 gm%). This is a correlation that might be expected since circumstances which impair albumin synthesis or cause increased loss or

Table 5 DIAGNOSTIC CONSIDERATIONS IN HYPOFERREMIA

	SI	TIBC	% SAT.	B.M. Fe Stain	RBC Indices
FeD Erythropoiesis	29 (16-48)	265 (210-350)	10 (5-16)	0 - Tr	N/N
FeD Anemia	28 (10-61)	346 (170-460)	7 (2-16)	0 - Tr	H/M
Anemia Chronic Disease	29 (18-48)	271 (200-358)	13 (7-19)	1+-4+	H/M
Normal	80-150	280-360	25-50		

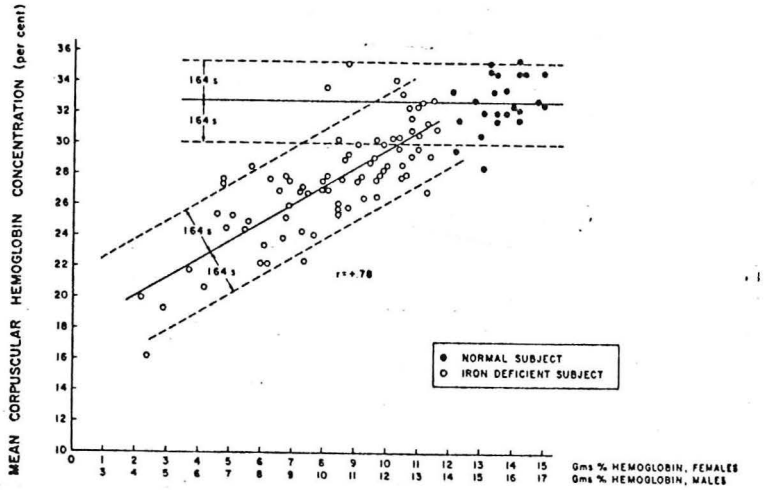
From Ref. 47
Values are mean and ranges

catabolism do so with transferrin as well (28-34) (e.g. protein depletion, renal or GI loss, infections and malignancy). Table 3 lists other tests in addition to bone marrow iron stains which might be considered to differentiate the ACD vs. FeD.

Heinrich has demonstrated that iron absorption remains the most sensitive and a nearly specific determinate of iron stores. (46) In patients who had the anemia of infections or malignancy, the iron absorption was normal despite hypoferremia unless they had histologic evidence of depleted iron stores. The only exception to the specificity of whole body iron absorption measurements is the presence of ineffective erythropoiesis or erythroid hyperplasia as seen in megaloblastic, sideroblastic or hemolytic states in which increased iron absorption may at times be seen.(8, 46) A decrease in liver or bone marrow content of non-heme iron is a specific means of differentiation but its sensitivity at the level of iron deficient erythropoiesis is unknown. Red cell protoporphyrin levels increase in circumstances associated with Fe deficient erythropoiesis (hypoferremia). (68-71) The sensitivity is limited by the delay of days to weeks in the development of abnormal values and more importantly, increases occur in the ACD as well. Its major application is in a retrospective diagnosis of iron deficient erythropoiesis since the values remain elevated for 2 months after institution of Fe therapy (until senescence of the majority of cells produced during the hypoferremic period). Serum ferritin studies of this stage of iron deficiency are still not clearly evaluable. Ferritin levels do not decrease in the ACD unless the patient is also iron depleted and thus are a very specific differential tool. (59) However, one study by Siimes et al suggested that 2/3 of patients with iron deficiency erythropoiesis had normal ferritin levels. (80) Jacobs et al noted that phlebotomy to iron deficiency produced a nearly simultaneous fall in ferritin and the % saturation to below 16%. (81) Further studies are required to define the sensitivity of this method.

Iron Deficiency Anemia - The classical final hematologic effects of progressive iron depletion is iron deficiency anemia. This stage is defined as the appearance in the circulation of hypochromic or microcytic/hypochromic erythrocytes in sufficient numbers as to produce abnormal red cell indices, as well as having all of the previously discussed parameters of iron deficiency. The magnitude of the anemia will reflect the degree of iron lack and the duration and rate of negative iron balance (blood loss). Thus, not only may iron deficient

erythropoiesis be present but a significant degree of anemia may exist due to iron deficiency with normal red cell indices. The only reason for separating this stage of FeD is to emphasize this fact. If one produces iron deficiency anemia by phlebotomy, the MCV falls prior to the MCHC but the development of an abnormal MCV follows the finding of an abnormal MCHC. (82) In large populations of patients with FeD anemia, therefore, the MCHC is more frequently abnormal, but may be normal with Hgb levels of 8 gm% or above in females and 10 gm% or above in males. (Fig 10) The MCV may be normal at any level of anemia. (83, 84)

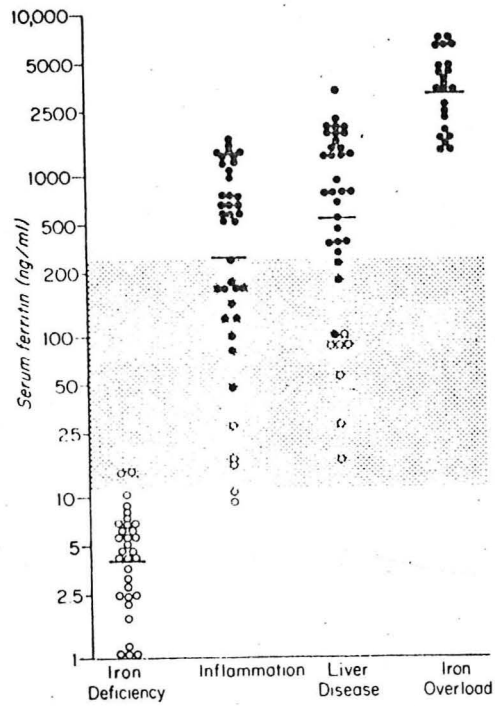


The relationship between mean corpuscular hemoglobin concentration and the blood hemoglobin level of 80 iron-deficient patients and 25 normal subjects.

Fig 10. Ref. 83

The red cell morphology also cannot be utilized as the decisive means of identifying FeD anemia. Although the classical picture of severely hypochromic, microcytic red cells with marked poikilocytosis is well known, a large number of patients with mild iron deficiency anemia will go unrecognized on peripheral smear examination by trained observers, whereas normal smears can likewise be interpreted as abnormal.(83) The serum ferritin level has been proven to be of greatest value in the patient with iron deficiency anemia. (35, 56-59) Fig 11 demonstrates that in FeD anemia the serum ferritin levels are almost always below 12 ugm/liter whereas in the ACD they are normal or elevated unless coexistent FeD is present. The major drawback to the routine use of serum ferritin for the differential diagnosis of FeD anemia, in addition to methodologic considerations, is that patients with "liver disease" will have normal values in the face of iron deficiency, presumably due to increased ferritin release from necrosed liver parenchymal cells.

In summary, the diagnosis of the progressive stages of iron deficiency requires the recognition of the sequence of events and physiologic and pathologic consequences of iron deficiency. Unless careful assessment of iron stores by histologic techniques and the serum iron levels are carried out or other more sophisticated methods of study are employed, over 50% of patients with iron deficiency will go unrecognized.



Measurements of Serum Ferritin in Uncomplicated Iron Deficiency, Inflammation, Liver Disease and Iron Overload.

Fig 11. Ref. 59

Differential Diagnosis of FeD Anemia

The differential diagnosis of FeD anemia includes, in addition to causes of hypoferremia discussed above, the causes of hypochromic and/or microcytic anemias not due to FeD. The hypochromic, microcytic erythrocytes of FeD reflect the decreased hemoglobin synthesis that results from the restriction of iron supply. Similarly, all other disorders associated with microcytic and/or hypochromic erythocytes are consequences of reduced hemoglobin synthesis - either defective heme synthesis or defective globin synthesis. Table 6 lists these conditions.

Table 6

CAUSES OF MICROCYTIC AND/OR HYPOCHROMIC ANEMIAS OTHER THAN IRON DEFICIENCY

A. Abnormalities of globin synthesis
   1. Thalassemias
   2. Hemoglobinopathies (e.g. Hgb. E, unstable hemoglobins)

B. Abnormalities of Heme Synthesis (Sideroblastic Anemias)
   1. Hereditary
   2. Acquired
      a. Primary idiopathic
      b. Secondary (e.g. lead intoxication, antituberculosis drugs, chloramphenicol toxicity, alcohol etc).

The single most important feature of these states as opposed to iron deficiency is that the serum iron and % saturation are normal or increased and iron stores are normal or increased. The disorders of globin synthesis are then specifically diagnosed by finding the changes characteristic for each condition by the appropriate hemoglobin studies. (85) The heme synthetic defects or sideroblastic anemias as a group are diagnosed by identifying the classical pathognomonic ringed sideroblasts on marrow iron stains. Further identification of the mechanism is then carried out. (86-88)

One final point relates to the coexistence of iron deficiency and other causes of anemia, most commonly nutritional deficiency of folic acid or vitamin B12. The megaloblastic pattern of the bone marrow may be masked and the serum iron, % saturation of TIBC and stainable iron in the bone marrow may be normal. The usual clue is to find hypochromic red cells in the B12 or folate deficient patient or to have an incomplete response to B12 or folic acid. (89-91)

Miscellaneous effects of FeD

A number of other, non-hematologic, effects have been ascribed to iron deficiency. Attempts have been made to demonstrate specific symptom complexes and performance impairment due to iron deficiency. (92) Well controlled studies have failed to demonstrate that such circumstances exist other than those symptoms directly attributable to anemia per se. (93, 94) On the other hand a number of observations have demonstrated that certain abnormalities do occur in a greater frequency in iron deficient individuals, mainly disorders of epithelial tissues. Table 7 lists some of these conditions.

Table 7

MISCELLANEOUS EFFECTS OF IRON DEFICIENCY

1. Glossitis (95)
2. Pica and Pagophagia (96, 97)
3. Gastric achlorhydria (98, 99)
4. Esophageal web (Plummer-Vinson Syndrome) (100)
5. Koilonychia (Spoon nails) (100)
6. Papilledema (101)

With the excpetion of glossitis and pica, these findings are rare and generally associated with severe and long standing iron deficiency. One other interesting proposal relates to an apparent increase in infections in iron deficient subjects, especially children. Attempts have been made to associate this debated observation to the effects of iron on microbial growth. (102)

The mechanism for these non-hematologic problems are unknown. A number of studies have demonstrated abnormalities of iron containing and non-iron containing enzyme systems and myoglobin. (103-106) To date there exists no data which would correlate these defects and any of the clinical derangements.

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Causes of Iron Deficiency

The diagnosis of iron deficiency is not, in itself, an end stage of patient evaluation. The etiology for the iron deficiency must be considered in each patient, and, if not readily apparent, must be sought. This apparently self-evident statement is often ignored. In one study from a university medical center it was found that such an evaluation was not carried out in 50% of iron deficient males. (134A) Table 8 emunerates etiologies which must be considered in the FeD subject. It is apparent that certain high risk categories

have a significant likelihood of developing some stage of iron deficiency and these should be the initial point of clinical or laboratory assessment.

Table 8 ETIOLOGY OF IRON DEFICIENCY

1. Menstrual blood loss
2. Gastrointestinal blood loss
3. Pregnancy
4. Inadequate Dietary Intake
5. Blood Donors and Diagnostic Phlebotomy
6. Urinary tract bleeding
7. Malabsorption - Subtotal Gastrectomy
8. Intravascular Hemolysis
9. Periods of rapid growth
10. Pulmonary hemosiderosis and Goodpasture's Syndrome
11. Hereditary Atransferrinemia

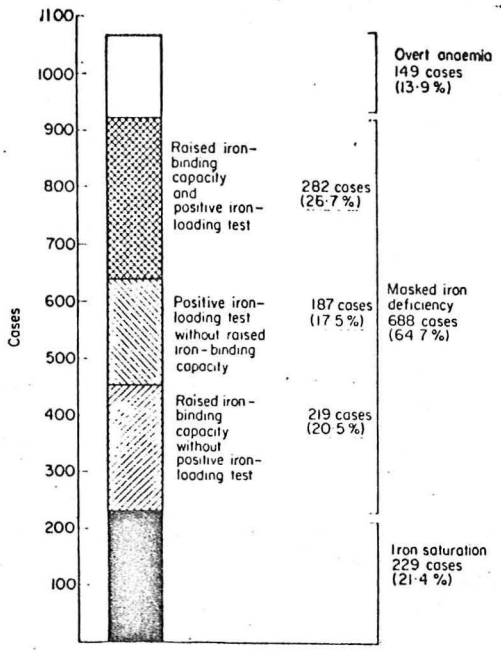
It will become apparent that the development of iron deficiency states may frequently be multifactorial, most commonly the balance of iron loss and iron intake being the critical determinant of whether FeD develops or what degree of iron deficiency exists.

Menstrual blood loss is the most common cause of iron deficiency in humans. When the more sensitive measurements of iron stores are used (B.M. iron stains and/or iron absorption), 30 - 40% of pre-menopausal women who have not had previous pregnancies or evidence of menorrhagia will demonstrate iron depletion, 5 - 10% iron deficient erythropoiesis and perhaps 1% frank iron deficiency anemia. (Table 9) When all premenopausal women are considered, 10 - 25% may have iron deficiency anemia and 2/3 have earlier stages of iron deficiency. Fig. 12. (43, 46, 107-109) The critical determinants of iron status in women appear to be quantity of blood loss and dietary intake of iron. When menstrual loss exceeds 80 ml/period and/or when dietary intake of iron is below 10 - 11 mgm/day, frank FeD anemia becomes very common. (46, 107, 110-113)

FREQUENCY OF PRELATENT, LATENT AND MANIFEST IRON DEFICIENCY IN GERMANY (HAMBURG) DIAGNOSED BY DEMONSTRATION OF INCREASED ^{59}Fe-ABSORPTION

	Prelatent (> 50% ^{59}Fe-absorp.)	Latent (< 60 µg% Fe in serum)	Manifest (< 12 g% Hb)	Total (%)
Females				
Menstruating (healthy)	34	6	~ 1	40
Pregnant, Trimester II	30	62	~ 1	92
Pregnant, Trimester III	14	72	14	100
Males				
Casual blood donors	45	10		55
Permanent blood donors (187 ± 58 ml blood/month)	90	10	~ 1	100

Table 9. Ref. 46



Observed frequency of iron saturation, masked iron deficiency and manifest anaemia in a non-selective sample of 1066 healthy women in Southern Germany.

Fig 12. Ref. 107

Gastrointestinal blood loss is the most common cause of iron deficiency in males and post-menopausal females. In these groups, the detection of iron deficiency at any stage should be considered to be due to this cause until proven otherwise. Certain misconceptions exist in the consideration of this etiology. A negative stool examination for occult blood does not eliminate the diagnosis of iron deficiency as a cause of anemia or eliminate blood loss as a cause of iron deficiency since the blood loss may have occurred in the past, be intermittent, or be of a magnitude less than the sensitivity of the test for occult blood. (114) Two frequently overlooked causes of overt or occult G.I. blood loss sufficient to induce iron deficiency are hereditary telangiectasia (115) and aspirin ingestion.(116)

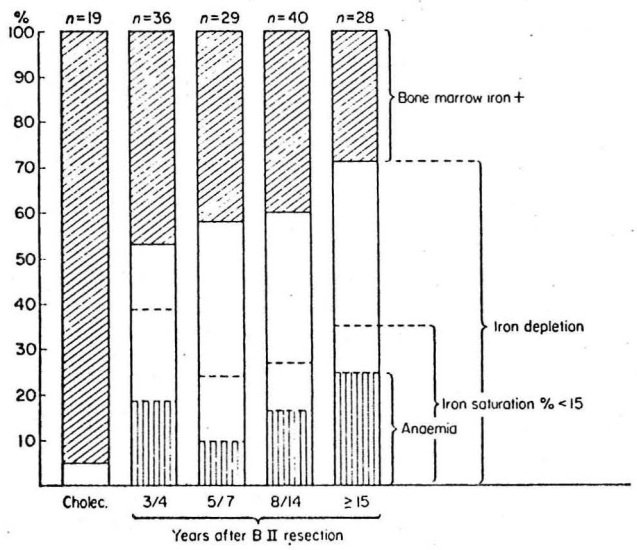
Pregnancy clearly is a major potential cause of iron deficiency. Estimates of iron requirements during pregnancy include 500 mgm for expansion of maternal RBC mass, 300 mgm for fetal needs and 200 mgm for maternal loss. Even with maximal iron intake from dietary sources and the reduction in menstrual loss during this period almost 100% of women will become iron deficient during pregnancy. (46, 53, 117) Table 9.

Inadequate Dietary Intake of iron is an extremely rare cause of iron deficiency in itself. If no iron intake occurs, the depletion of normal stores in a male would take approximately 2-3 years and the normally menstruating female 1-2 years. However, this factor contributes significantly to the probability and the rate of development of iron deficiency in high risk groups, such as pre-menopausal females, children in rapid growth periods, pregnant females, and chronic blood donors.

Blood Donors have been repeatedly shown to have smaller measurable iron stores than individuals of the same age and sex. (38, 46, 134) Table 9. The significance of diagnostic phlebotomy during hospitalization as a cause of blood loss anemia and depletion of iron stores should not be overlooked. Data does not exist regarding the magnitude of this problem.

Urinary tract bleeding uncommonly is large enough in quantity or duration to induce significant iron deficiency. When this occurs, the cause is obvious by history because of the obvious nature of the urine color. This is a classical consequence in patients with recurrent hematuria in hemophiliac syndromes and sickle cell trait, however. (118)

Malabsorption of Iron as a cause of iron deficiency is very rare. It is generally seen only in patients with loss of or disease of the iron absorptive portion of the small intestine, (i.e. duodenum and proximal jejunum), the sprue syndromes being the most reported setting. Patients who have previously undergone subtotal gastrectomy are the most common exception to the rule, however. Iron deficiency of varying degrees occurs in a large percentage of these patients. Up to 70% of patients previously undergoing a subtotal gastrectomy have some degree of iron deficiency and approximately 25-33% have anemia due to iron deficiency. (119-122) Fig 13. The majority of patients will be recognized by 2-4 years post surgery.



Bone marrow iron in nineteen males after cholecystectomy compared with bone marrow iron in 133 males who underwent partial gastrectomy (Polya-Hofmeister or Billroth II modification) three to more than fifteen years before.

Fig 13. Ref. 122

A number of studies have demonstrated that the mechanism of the anemia is multifactorial.(Table 10)

Table 10

PATHOGENESIS OF IRON DEFICIENCY AFTER SUBTOTAL GASTRECTOMY

1. Blood loss prior to surgery
2. Continued blood loss
3. Malabsorption of Food Iron
   A. Rapid transit
   B. Achlorhydria

A majority of patients had blood loss leading to the gastrectomy. In most instances, appropriate replacement of the iron depletion was not accomplished. Blood loss continues after surgery. By Cr 51- tagged RBC methods, Kimber et. al. demonstrated that 6/8 patients had excessive blood loss averaging 4 ml/day with a range of 0 - 28 ml. (123) This is 1-3 ml. more per day than normally found. This degree of blood loss is usually accompanied by negative tests for occult blood in the stool and almost invariably the feces are not discolored. (114) This requirement for an additional 2 mgm of iron per day or more can often be met by patients who have an intact stomach on good dietary intake. However, these patients have an impairment of absorption of food iron. There is no ability to enhance absorption of iron from food sources in patients with a subtotal gastric resection who become iron depleted. (9, 119, 123, 124) This most likely represents both a loss of the pouch function of the stomach which allows appropriate preparation of iron for absorption, bypass of part of the absorptive area, and, in some patients, a reduction in the acid media which promotes iron solubility and pepsin activity (123, 125-128) It should be noted, however, that the absorption of medicinal iron in these patients can be enhanced adequately to allow oral repair of the iron deficiency. (123, 124)

The other causes of iron deficiency listed in table 8 are rare but should be considered when the etiology is unclear.

Chronic intravascular hemolysis due to red cell fragmentation on prosthetic heart valves(129) and in paroxysmal hemoglobinuria (130)are well documented causes of FeD. In these circumstances, the kidneys contain large quantities of iron but it is not available for reutilization.

Idiopathic pulmonary hemosiderosis and Goodpasture's Syndrome represent two other diseases in which parenchymal deposition of iron occurs in a site which makes it unavailable for reutilization. (13, 132) Hereditary atransferrinemia also is not a circumstance of total body iron depletion but one in which iron deficiency anemia occurs with iron overload due to the lack of the iron

transport protein - transferrin. (133)

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Therapy

The presence of iron deficiency usually requires therapeutic intervention if repair is to be accomplished. Even when the mechanism of negative iron balance has ceased, long periods will be required to restore normal iron status from dietary sources alone. Data suggest that from a diet which contains optimal amounts of iron, a maximum increase to 3 - 4 mgm absorbed per day can be expected (64, 135 - 139). The ceiling is a result of two factors - a) Complexing of food iron and b) Dose-absorption dependence. Fig 14 shows that as increasing doses of iron are ingested, the total absorbed increases but the % decreases with a log-log relationship. The effect of the type of food containing iron on its absorption is shown in table 11. An equivalent dose of medicinal iron would be absorbed in the 20-30% range.

ABSORPTION OF ISOTOPICALLY LABELED FOOD IRON IN NORMAL SUBJECTS

Reference	*Form of Iron*	*Amount of Iron (mg.)* °	*Number of Studies*	*Method*	
				Stool	*Blood*
Callender *et al.* [20]	Raw hemoglobin	5	10	15	10
	Cooked hemoglobin	5	10	10	7
	Raw hemoglobin and corn flour	5	7	12	17
Chodos *et al.* [27]	Egg	6 (4–8.6)	14		1.4
	Chard	3.5	4		1.2
	Beet greens	3	2		0.8
Schulz [122]	Milk	0.3	6	2.8	
Moore [106]	Eggs	3.5	8	4.0	
	Chicken muscle	9	5	11.0	

° Average figures used when individual doses varied.

Table 11. Ref. 136

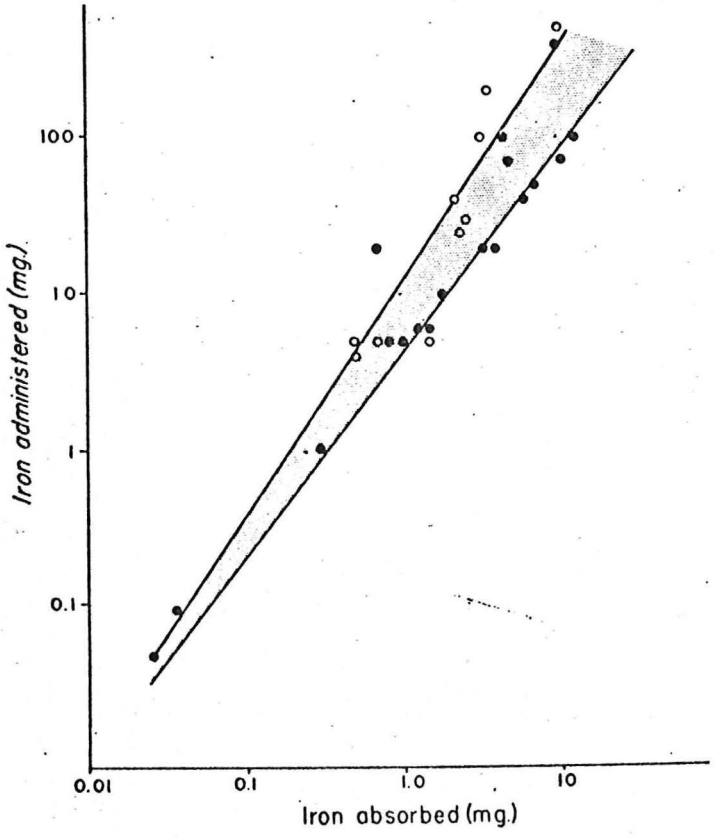


Fig. 14. Ref. 136

Debate does exist over whether iron depletion alone should be treated since no evidence exists that this stage in itself is harmful or associated with symptoms (see above). The prevalent view is that such a patient is more prone to develop physiologically significant iron deficiency if further negative balance ensues and thus is a candidate for repair of iron stores.

Oral Iron Therapy

In the vast majority of iron deficient patients, oral therapy will accomplish normalization of hemoglobin levels and iron stores. (46) Optimal iron therapy must take into account many variables which are listed in table 12.

Table 12 CONSIDERATIONS IN ORAL IRON THERAPY

1. Chemical form of iron
2. Dosage and Frequency
3. Side Effects
4. Effect of Food and Antacids
5. Pharmaceutical properties
6. Absorption promoters
7. Duration of Therapy
8. Cost

Fig 15 demonstrates the relative absorption of various chemical forms of iron at equivalent quantities of elemental iron. (140) Because of solubility characteristics, ferrous salts are superior. Of the chemical forms available on the American market, ferrous salts of sulfate, fumarate and gluconate are essentially equivalent and maximally effective.

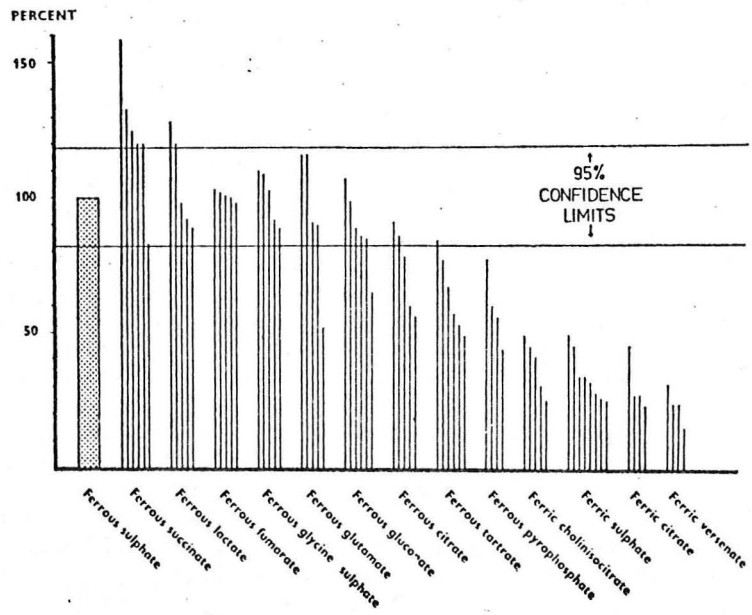


Fig 15. Ref. 140

As noted above, iron absorption related to dose has log-log characteristics. Theoretically massive doses would be most effective. However, side effects increase in frequency when single doses exceeding 50-100 mgm of elemental iron are administered. (141,142) In addition, as the frequency of doses increases up to at least 4 per day, the total Fe absorbed per day increases. (140) Although frequently overemphasized, side effects of oral iron therapy do occur. Some studies have suggested that the frequency is no greater than with placebo. (143) In the largest and most carefully performed study, however, a statistically significant increase in side effects over placebo was found. (142, 144) Fig 16. While receiving placebo 12% had complaints while 25% receiving ferrous salts noted side effects. Those side effects occurring more frequently in the treated group were nausea, epigastric pain, diarrhea or constipation.

In an attempt to reduce these side effects, it has been recommended that iron be given with food or antacids. It must be emphasized that food and alkaline pH both significantly decrease iron absorption. Ferrous salts, given with food are absorbed as if the iron were intrinsic to the food, and thus the absorption may be decreased several fold. (13)

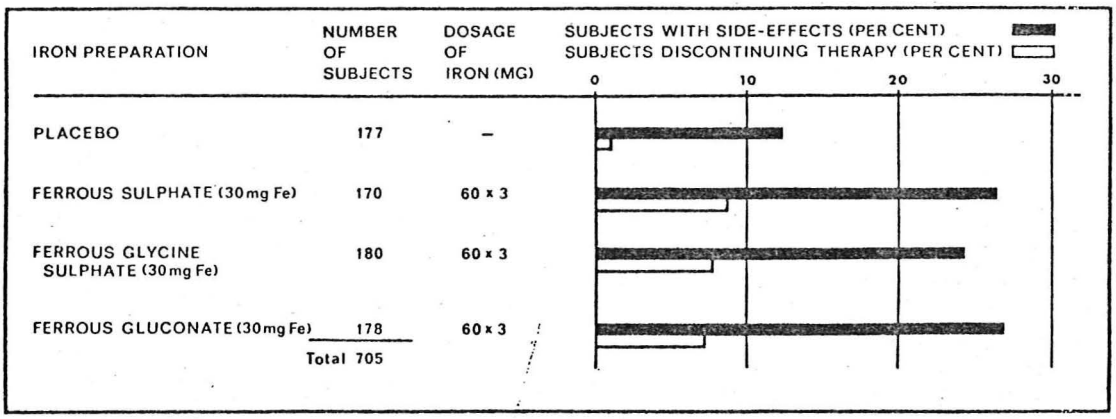


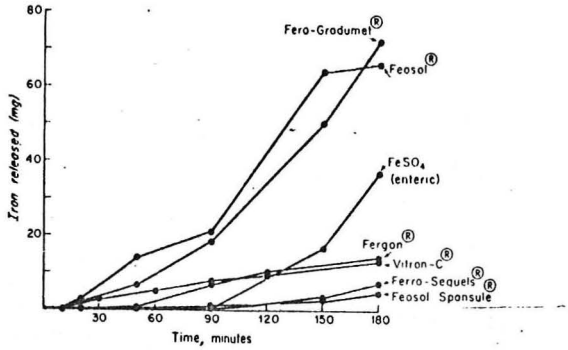
Fig 16. Ref. 144

Another approach to reducing side effects has been to produce various pharmaceutical modifications which will cause a sustained release of iron intending to reduce high concentrations in the stomach. Since iron is absorbed primarily from the duodenum and upper jejunum, delay of availability until the preparation is beyond these sites would negate therapeutic effectiveness. Ferrous salts in tablet form are dissolved and available for absorption in minutes. (144) The rate of dissolution of many sustained release preparations is quite variable. (Fig 17) It is probable that unless most of the iron is available in less than three hours, the preparation will be suboptimally effective for a given dose. Such preparations can be effective but well controlled absorption studies are not available for most. (103, 145)

It has been demonstrated that absorption of a given dose of a ferrous salt can be altered by the presence of various complexing substances. (146) Most likely this relates to the effect of these agents on the availability of iron for uptake by the mucosal cell. (15) The most effective substance which promotes absorption is ascorbic acid, which will increase absorption not only from iron salts (144, 146) but also food. (137) Significant effect, however, probably requires a 10 fold or greater molar excess of ascorbate over elemental iron, most likely because of the formation of different types of

Fig 17 Ref.103

Dissolution rates of various commercially available oral iron preparations in acidic (pH 2.0 or less) gastric juice. Very similar results were obtained in achlorhydric gastric juice and in fluid obtained by perfusion of normal human duodenum. In each, release of iron from Feosol Spansule, Ferro-Sequels, Vitron-C, and enteric-coated ferrous sulfate was poor with up to 3 hr of incubation. Other preparations had released 80 to 100 percent of their iron content within 3 hr in each of these media. Iron release from Fergon was poor in acidic gastric juice but relatively rapid in other media tested.



complexes at different molar concentrations. (146, 147) Several preparations are on the market using this additive, but ratios of ascorbate to iron are often less than 10 to 1.

Duration of therapy is a difficult problem to answer since iron absorption rates appear to progressively decrease with increasing repair of iron deficit. Heinrich has utilized bone marrow iron stains and whole body iron absorption measurements to serially evaluate repair of iron deficiency. (46) A summary of his data is shown in table 13. Oral iron was administered as ferrous sulfate, 50 mgm elemental iron per dose, twice daily. Once anemia was corrected and evidence for iron deficient erythropoiesis was absent (normal % saturation of TIBC), a total dose of 6-9 grams more was necessary to normalize all parameters. (60-90 days at 100 mgm elemental iron/day. Obviously if a continued loss of iron exists, the duration will be increased or permanent supplementation may be necessary.

COMPARISON OF EXISTING IRON DEFICIT AND TOTAL AMOUNT OF THERAPEUTICAL IRON REQUIRED FOR FILLING UP THE IRON STORES (NORMALIZATION OF DIAGNOSTIC ^{59}Fe-ABSORPTION) IN PRELATENT, LATENT AND MANIFEST IRON DEFICIENCY

	Existing iron deficit (g)	Total amount of required therapeutical iron intravenous Fe (g)	absorbed iron (g)
Prelatent iron deficiency	~ 0·8	0·5–1·0	0·7–1·0 (6–9 g)[a]
Latent iron deficiency	~ 1·0	1·0–1·5	~ 1·0 (9 g)[a]
Manifest iron deficiency	2–3	2·0–3·0	1·3–2·0 (12–18 g)[a]

[a] Total therapeutic iron dose (given orally).

Table 13. Ref. 46

Cost of therapy cannot be minimized. There are over 100 iron-containing preparations listed in the 1975 PDR. Only 15 are preparations of iron salts of sulfate, gluconate or fumarate alone. There is no excuse for the administration of preparations containing other hematinics. It will be

rather uncommonly necessary to use sustained release capsules or ascorbate containing compounds. Table 14 lists the comparative costs of some commercially available iron preparations.

Comparison of some oral iron preparations

Preparations	*Iron content (mg per pill)*	*Approximate cost to patient (dollars per month of treatment)**
Single agents		
Ferrous sulfate	60	$ 2.00
Ferrous gluconate	37	2.00
Ferrous fumarate	66	2.50
Prolonged-release and enteric-coated		
Ferrous sulfate Enseals	66	2.50
Fero-gradumet	105	4.50
Feosol Spansule	45	8.80
Ferro-Sequels	50	8.25
Ferronord DLA	75	14.50
Mol-Iron Chronosule	78	7.40
Combination hematinics		
Geritol	50	9.00
Iberol	105	4.70
Perihemin	55	8.00
Trinsicon	90	5.00
Simron	10	43.00
Vitron-C	66	2.75
Fero-grad-500	105	4.50

*On the basis of dose adequate to provide 180 to 230 mg of elemental iron per day. Each cost entry includes "compounding fee" or equivalent retail markup where applicable. Since this price markup may vary considerably from one pharmacy to another, the prices quoted should be considered only as approximations. They are based on American Druggist Redbook, 1971.

Table 14. Ref. 103

Oral iron administration has been advocated as another diagnostic tool which is inexpensive and harmless to the patient. In the presence of pure iron deficiency anemia with no coexisting mechanisms for anemia or lack of adequate erythropoiesis, such a therapeutic trial may be valid. Another parameter of evaluation must be considered - the rate of response to oral iron in iron deficiency anemia is inversely related to the degree of anemia. (140, 148) Standard textbooks state that a rise of 0.2 gm Hgb/100 ml per day can be expected. However, the rate will be much less at initial hemoglobin levels of 9 gm% or greater (0.1 gm/day). Thus an appropriate duration of the therapeutic trial must be employed before a lack of response can be considered.

A final point regarding oral therapy relates to the patient whose anemia apparently fails to respond when the correct diagnosis of iron deficiency has been made. The most common explanations are listed in table 15.

Table 15 CAUSES OF FAILURE OF ORAL IRON THERAPY

1. Patient non-compliance
2. Continued blood loss
3. Administration with meals or antacids
4. Other mechanisms of impaired erythropoiesis

These are listed in order of frequency in our experience. Malabsorption due to mucosal abnormalities is not listed. It is as rare as it is a cause for iron deficiency initially.

In summary, when the diagnosis of iron deficiency has been correctly made and the etiology appropriately sought, oral iron therapy is the treatment of choice. It is recommended that a ferrous iron salt be given, 50 - 100 mgm elemental iron per dose, 2-3 times daily. This should be continued for 2 - 3 months beyond the correction of iron deficient erythropoiesis (or longer if continued blood loss exists). If side effects occur, the use of ascorbate containing preparations given with meals or a sustained release preparation with good dissolution characteristics (fig 17) be considered. If a failure to respond is noted after 4 weeks of therapy, one of the reasons listed in table 15 should be sought.

Parenteral Iron Therapy (55, 149-151) Iron preparations for parenteral use are available. They have the advantage of giving a predictable quantity of iron which will repair the anemia present and replete the iron stores as well. The dependence on patient compliance is avoided, particularly where several months or longer of oral iron therapy is necessary to replete stores. These preparations are not without side effects including pain at the injection site, cosmetic discoloration of the skin, and rarely, anaphylactic-like reactions. The question of local carcinogenicity has not been settled but if it exists, it is very rare. In addition, the availability of parenteral iron for erythropoiesis is incomplete.

The comparative rate of response of iron deficiency anemia to both adequately employed oral therapy and parenteral therapy is essentially equal.

No emphatic statement regarding the indications for parenteral iron can be made. Each case dictates its own considerations, and if all parameters that have been discussed in this presentation are taken into account, then clinical judgment must be the final arbiter.

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Prophylaxis of Iron Deficiency

Since the problem of iron deficiency appears to affect a large portion of our population, the question of prevention of the problem is a reasonable consideration. Two distinct methods of prophylaxis are apparent.

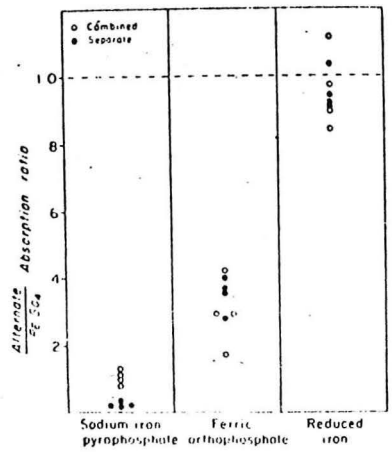
1. Treatment of high risk groups with medicinal supplements.
2. Afford significant iron from dietary sources by fortification

of selected food products.

The former approach is reasonable since only those persons requiring increased iron intake would be affected. Obviously the limitation is that the practical application of this method requires physician contact by otherwise healthy individuals and a high level of awareness on the part of the physician. Nevertheless, this approach is commonly utilized today in pediatric care of newborn children and in the care of pregnant females. Less attention is paid to the menstruating female, the chronic blood donor or patients having undergone subtotal gastrectomies.

Since World War II certain grain products (white flour, white bread and selected bakery products) have been fortified with iron in the U.S. Because of the seemingly high prevalence of iron deficiency in children and pre-menopausal women, in 1972 the FDA, supported by the Council on Foods and Nutrition of the A.M.A., proposed increasing the level of fortification nearly three fold in those products (e.g. from the present 13-16.5 mgm Fe/lb to 40 mgm/lb in enriched flour). (152) A number of knowledgeable persons in the field of hematology raised serious questions regarding this proposal. Since that time, no action has been taken on the proposal and little has been done (or perhaps can be) to settle the controversy. Some of the questions asked are as follows. a) What is the actual prevalence of iron deficiency in the U.S? Studies discussed in earlier sections of this protocol indicated incidences of various stages of iron deficiency in selected population groups. All studies aimed at answering the question in greater depth have dealt only with iron deficiency anemia. The criteria in some studies have either been poor (153) or some high risk groups (e.g. menstruating females) have not been evaluated. (154) The best study to date, using serum iron levels, suggests that iron depletion or iron deficiency anemia is present in 2% or less of females ages 18-44 and is not related to race (155) This is quite similar to the studies noted above. b) What foods should be fortified? A study of eating habits in this country does support that wheat and wheat products are the most universally utilized food - 98% of women, for example, ingest such foods on any given day. (152) Milk product fortification has also been proposed, aiming at the growing child. (156) c) What kind of iron source should be utilized? A commission of the Life Sciences research office, FASEB, was established to answer the question of bioavailability of iron from cereal foods. Their report published in July 1974 revealed several startling findings. (157) There was no control of the type of iron supplementation by the FDA. Ferrous sulfate, known to be the most bioavailable source, was used in less than 20% of products fortified because of effects on storage properties. A study performed by Cook et. al. to answer this question revealed that only ferrous sulfate and finely grained reduced elemental iron powder were significantly available for practical use, and that the reduced iron presently employed in fortification was too large grained. (158) Thus 80+% of iron fortification today is not of value! d) How much iron should be added? Based on the preceding statements, this question becomes superfluous until a standard means of fortification is established. Estimates of effect of fortification, based upon optimal absorption (ferrous sulfate standards), suggest that the increment in iron intake suggested by the FDA may be appropriate. (159) No actual data is available. e) Would the fortification be effective? One well controlled study of iron fortification of bread has been carried out on a large population group. Its results do not answer the question since the period was too short (20 months) and the only parameters sought were <u>improvement</u> in hemoglobin levels, Hct and MCHC. (160) f) What will be the possible harmful effects of food fortification on groups at potential risk for iron overload (idiopathic hemochromatosis, alcoholics, thalassemia and sideroblastic states?)

Fig. 18, Ref.157



A FASEB commission concluded that this question cannot be answered from a practical clinical experimental design. (152) Estimates are that less than 10% of males would ingest more than 65 mgm of iron daily from the proposed levels of fortification. (159) It is known that 100 mgm/day or more iron intake with alcohol in Bantus induces iron overload. (161) On the other hand ingestion of up to 500 mgm of dietary iron in other population groups does not appear to cause iron overload. (162, 163)

Thus the need for or feasability of iron fortification as well as its potential harmful effects is not presently known. Until more information is available (if ever), the responsibility of searching for and preventing iron deficiency remains with the medical profession.

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