Iron Kinetics with Emphasis on Iron Overload

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BODY IRON IN MAN is estimated at 35 to 45 mg/kg or a total
of about 3 g.[1] The major portion of body iron, some 30 mg/kg, is held
in the circulating red cell mass and erythroid marrow as hemoglobin.
The only other fraction of quantitative significance is storage iron,
amounting to another 15 mg/kg in the adult male and varying from 0
to 10 mg/kg in the female. The manner in which body iron is main-
tained and its movement within the body become important in
understanding anemia and iron overload states. For the purposes of this
discussion, three aspects of iron exchange will be considered: exchange
between man and his environment, internal iron exchange and, more
specifically, storage iron exchange.

External Iron Exchange

Iron losses in man are so limited that they are most accurately deter-
mined by prolonged studies of the turnover of ^{55}Fe in the red cell mass.[2]
The normal loss of about 0.9 mg/day in the adult male calculated by
this technic is derived from the gastrointestinal tract (0.6 mg), from
the skin (0.2 mg) and from the urinary tract (0.1 mg).[3] These losses
are moderately affected by the status of iron balance; in iron de-
ficiency they are decreased to perhaps 0.5 mg/day and in iron overload
the loss may increase to 2 or at the most 3 mg/day.

Since man maintains a precise iron balance during adulthood, it
follows that *iron absorption* in the normal male is about 0.9 mg/day.
This iron is absorbed from a diet containing 10 to 20 mg of iron (6 mg/
1000 calories), so that the overall absorption of iron is at a level of
about 6%.[4] The principal determinants of iron absorption are: a) the
amount and type of food iron consumed and b) the behavior of the
intestinal mucosa. The amount of food iron ingested is largely deter-
mined by the physical activity of the individual, and its availability

relates to the type of food ingested, particularly the amount of animal muscle. Mucosal regulation of absorption usually reflects a state of body iron balance and functions to maintain this within normal limits.

Iron stores appear to reflect the ratio between available iron in the diet vs requirements, and therefore may be used as an index of iron balance. Thus, man with his average intake of 16 mg/day and requirements of 0.9 mg/day equilibrates at about 1000 mg iron stores and shows a dietary iron absorption of about 6%. He has a three- to four-fold margin between basal and maximal absorption and an ample cushion of iron reserves to protect against sudden demands; therefore, nutritional iron deficiency rarely occurs in the male. In the menstruating female with an intake of 11 mg of iron per day and requirements of 1.3 mg, mean iron stores are about 400 mg and absorption is about 12%. Maximal absorption is less than two times basal, and some women have menstrual losses which consistently approach and occasionally exceed their maximal absorptive capacity. This borderline balance is reflected in the absence of iron stores in approximately a third and the presence of "nutritional" iron deficiency anemia in 5 to 10% of the adult female population. In all pregnant females, the needs of the last trimester exceed the iron which can be absorbed from diet. Thus, iron appears unique in human nutrition as a substance which cannot be procured in adequate amounts from an otherwise normal diet by a large segment of the population. To be emphasized are the extremely limited amounts of iron available through diet and the considerable period of time required to modify iron balance through normal processes of absorption or loss.

Internal Iron Exchange

The pathways of *iron exchange within the body* are well defined [5] (Text-figure 1). The plasma protein, transferrin, mediates iron ex-
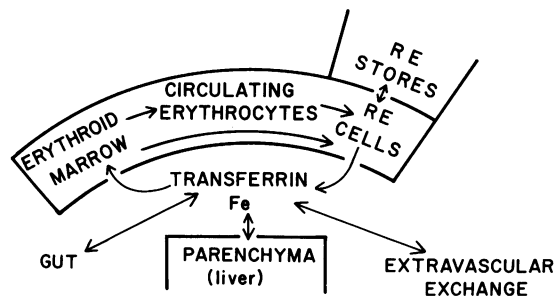
TEXT-FIG 1—Pathways of internal iron exchange.

change from one tissue to another. The major exchange involves red cell turnover. Most erythrocytes are destroyed within the reticuloendothelial cell, and there is a continuous movement of iron from RE cells to the immature erythroid cell of the marrow. This is a one-way flow, and virtually no transferrin-bound iron is passed in the reverse direction. Recently, another pathway of heme catabolism has been demonstrated.[6-8] Haptoglobin-bound hemoglobin, heme-hemopexin and ferritin are taken up predominantly by the hepatocyte. Thus, in certain hemolytic states involving either developing or mature red cells, it is possible that appreciable amounts of iron may pass directly from the lysed red cell to the hepatic parenchyma. The other important pathway to be considered is exchange between transferrin iron and parenchymal iron stores, particularly those of the liver.

Quantitative estimates of iron exchange along these pathways in man have been made through an analysis of the disappearance curve of transferrin-bound radioiron. Plasma iron so complexed has been demonstrated *in vivo* to behave as a single homogeneous pool.[9,10] However, the disappearance curve is a complex one, with at least three components, indicating at least two identifiable refluxes. A recent study [11] has separated iron which becomes fixed in tissues from reflux iron. It has been further possible to identify the major components of both fixed and reflux iron. For example, the rapid reflux was shown to represent a lymphatic circuit in which the transferrin iron complex enters the extracellular fluid and returns to circulation without dissociation.[12] The slow reflux disappeared when there was no erythroid marrow and thus is presumed to represent the wastage iron of erythropoiesis.[11] The amount of iron involved in exchange in the normal individual, calculated from this analysis of the plasma iron curve, is shown in Table 1. It is apparent that most of the "action" of iron exchange is normally concerned with the erythron, and that the normal rate of turnover may be increased manyfold in certain anemic states. The capacity to deposit transferrin iron as ferritin and hemosiderin in body tissues (parenchymal storage) is at most 25 mg/day. Kinetic

Table 1—Internal Iron Exchange in a 75-kg Man

|	Percent	mg/day	Disease
Total (PIT)	100	37.5	—
Erythron	80	30.0	0–300
Parenchymal	12	4.5	0–25
Lymphatic	8	3.0	0–15

studies [11] have established that the amount of transferrin iron loaded
into parenchyma at any one time may be predicted from the amount of
transferrin iron in the blood (Text-figure 2). The relationship may be
expressed by the formula:

Parenchymal iron uptake (mg/day) =
plasma iron (mg%) $\times$ plasmatocrit $\times$ blood volume (ml) $\times$ 0.0021

Storage Iron Exchange

Normal iron stores are distributed approximately equally between
the liver, striate muscle and reticuloendothelial system.[13–15] They are
composed of ferritin (two-thirds) and hemosiderin (one-third).[16,17]
Under basal conditions, their exchange appears limited. One way of
evaluating mixing is to follow the specific activity of the red cell mass
after an intravenous injection of radioiron.[2,3] An initial rapid fall
component is seen over the first year. If this is assumed to represent
dilution of iron into body stores, a mean figure of 600 mg of stores
may be calculated in normal male subjects; this is about 60% of the
stores which may be demonstrated by phlebotomy.[18] It may be specu-
lated that this mixing represents a slow exchange with the ferritin
pool, but that hemosiderin stores do not mix.

Both ferritin and hemosiderin are available for the needs of red cell
production and may be fully mobilized over a period of several months
by phlebotomy. The rate of iron mobilization is related to total body
iron stores, and in the average male subject about 30 mg/day may be
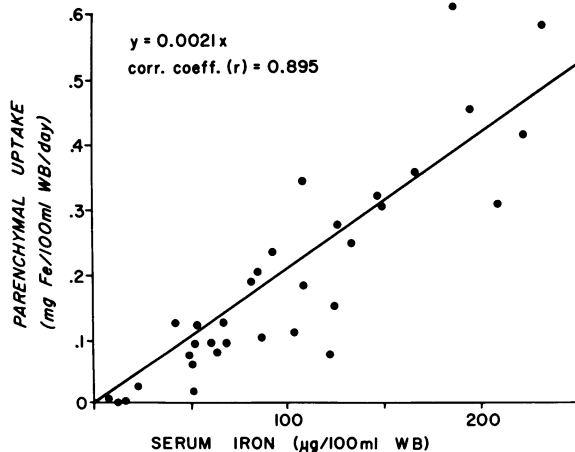
TEXT-FIG 2—Parenchymal iron loading.

initially mobilized. This is sufficient to increase red cell production to twice the basal level.[19] In the presence of a hemolytic process, or when phlebotomy is carried out with return of nonviable cells, production may be increased to four to six times the basal level within a week.[5,20] Thus, the erythroid marrow is capable of using far more iron than is commonly mobilized from body stores after iron loss has occurred. Although limited, iron mobilization from stores is in turn more than ten times that available through food iron absorption.

Iron overload may be created by the parenteral injection of iron (transfusion of blood or therapeutic iron injections), by a disorder in the mucosal regulation of iron absorption which lets in an inappropriate amount of iron, or by unusual conditions of high oral iron intake.[1] Given an overload state, the important distinction is the location of the excessive stores. Either reticuloendothelial (RE) or parenchymal deposits may predominate; RE deposits appear innocuous, while parenchymal deposits of long standing and sufficient size give rise to the clinical manifestations of hemochromatosis. The deleterious effect of parenchymal iron overload is clearly demonstrated by the reversibility of organ damage, especially cardiac failure, and improvement in survival of patients with idiopathic hemochromatosis whose iron deposits have been removed by phlebotomy.[21]

Central to the problem of hemochromatosis is, therefore, the *way* in which the internal distribution of iron is regulated. It is clear that RE siderosis results from retention of iron from catabolized red cells at their site of destruction. This retention is exaggerated by inflammation, in which the release of iron from the RE cell is blocked and at the same time a hypoferremia prevents hepatocyte loading. Parenchymal loading from transferrin, on the other hand, is related to the plasma iron concentration as discussed previously. Interesting differences, however, are seen in adult patients with refractory anemia depending on the degree of erythroid marrow proliferation.[1] With aplastic anemia in the adult, RE overload due to transfusion is marked, whereas parenchymal overload is minimal and fibrosis of the liver is rare. In a literature review of 20 autopsy patients receiving over 100 transfusions, cirrhosis was recorded in only one. Despite fewer transfusions, 31 patients with refractory anemia but a hyperplastic marrow showed heavy parenchymal deposits, and cirrhosis was present in 26.[1] Possibly, the direct hepatocyte loading of hemoglobin and ferritin iron released into the plasma of these patients as a consequence of their ineffective erythropoiesis made the difference.

From the standpoint of iron kinetics, there is no real distinction between parenchymal loading in the patient with idiopathic hemochromatosis and parenchymal loading occurring in other patients with an iron-saturated transferrin, whether caused by liver disease, aplastic anemia or chronic renal disease with transfusion.[11] The same formula for estimating parenchymal iron overload from plasma iron turnover and plasma iron applies in all these conditions. Similarly, parenchymal stores from any cause may be mobilized by phlebotomy (unless severe anemia precludes bleeding). Thus, parenchymal overload appears to be a passive phenomenon in all instances, depending on the amount of transferrin iron brought to the liver rather than any abnormal tissue affinity for iron. The toxicity of parenchymal iron is assumed to relate to the amount of iron loaded. This can be visualized by liver biopsy or more simply evaluated by desferrioxamine. We have previously shown the correlation between urinary iron excretion produced by an intramuscular injection of this substance and parenchymal stores.[22] More recently, Hershko and Cook have demonstrated more directly in the rat that the iron mobilized by desferrioxamine is derived specifically from hepatocyte ferritin.[23]

Further research remains to be done to learn more about the determinants of a) the flow of iron across the intestinal mucosa which controls total body iron and b) regulation of plasma iron level which controls the distribution of storage iron between RE and parenchymal cells.

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