The Treatment of Iron Deficiency Anemia

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THE INTEREST OF THE PHYSICIAN in iron deficiency anemia is in part ascribable to its frequency and to its curability by specific therapy. Of further concern, however, is the knowledge that this anemia in the adult is usually due to blood loss and that occult bleeding may be the first manifestation of more serious underlying disease. Studies in recent years provide a practical understanding of iron metabolism from which the pathogenesis, diagnosis, and treatment of iron deficiency anemia may be reviewed. Special consideration is given to the use of parenteral iron in treatment.

Iron Metabolism and the Pathogenesis of Iron Deficiency Anemia

Exchange of iron between man and his environment is small, and iron excretion is of little importance in determining iron balance. The cumulative daily loss in urine, stool, and from skin surfaces is estimated at 1 mg. or less and cannot be greatly increased. Iron absorption, on the other hand, appears to play a more active role in regulating body iron. For example, Hahn et al. have demonstrated in man a 5–15 fold increase in absorption of iron salts in the iron depleted, as compared to the normal dog. In the patient it is doubtful whether absorption of iron from the diet varies over so great a range or is always consistent with the needs of the body. Dietary iron is less well absorbed than iron salts, and from an average diet, containing 10 to 30 mg. iron, the range of compensation to body needs would be less than 1 mg. in the normal male to at most 3 or 4 mg. in the iron deficient.

There are peaks in iron requirement through life. In infancy an excess of about 200 mg. is required to meet the needs of an expanding red cell mass and rapid tissue growth at a time when dietary iron is limited. This requirement is much greater if the infant is born prematurely. During the accelerated growth phase of adolescence a second peak occurs with a requirement of 200–300 mg. per year. Menstruation usually requires a replacement of 150–300 mg. annually. During nine months of pregnancy an estimated 500 mg. may be lost and during six months of lactation an additional 150 mg. These are the stress periods in iron...
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metabolism. The greater frequency of iron deficiency anemia in infancy, adolescence, pregnancy, and with menstruation indicates how often these extra requirements of 1 to 2 mg. per day exceed the amount which the individual can absorb from his diet.

Iron deficiency anemia is the result of a deficit in available iron, i.e., iron absorbed from diet plus iron reserves within the body, as compared to the iron requirements of the individual. In infancy there is a close relationship between diet and iron deficiency. The iron stores created at birth by deposition of red cell iron in tissues are exhausted by the third or fourth month while iron requirements from growth remain large, and an iron deficient diet will result in anemia by the fifth or sixth month. The adult, however, has usually managed to establish an iron surplus or reserve,* gradually accumulated through childhood and adolescence. The dietary iron requirements of the adult have been estimated at 1 mg. or less per day in the male and 1 to 2 mg per day in the menstruating female. Thus the adult with an excess of body iron and with minimal daily loss of iron, becomes relatively independent of iron intake. In the adult, iron deficiency anemia is ascribable with few exceptions to blood loss and does not occur from dietary deficiency. When bleeding occurs, its impact on the hematopoietic system will be largely determined by the adequacy of iron stores. The regeneration of 500 ml. of blood is accomplished in 1 to 3 weeks if tissue iron is available but requires three months or longer when iron must be assimilated from diet.† Thus the degree of anemia following bleeding will be determined by the lifetime iron balance of the individual as reflected in the amount of storage iron.

A sequence of events occurs in the development of iron deficiency (fig. 1). Where a negative iron balance is created through blood loss, pregnancy, or growth, iron is first mobilized from the iron reserve. This reserve† represents about 1000 to 1500 mg. of iron in the adult male,§ and probably less in the female.‖ Following the depletion of these stores, the serum iron falls, and iron granules disappear from the cytoplasm of maturing normoblasts.‖ Hemoglobin synthesis is retarded, and with the deficiency of iron an excess of protoporphyrin accumulates within the erythrocyte.‖ After several months, shape alterations appear in the circulating erythrocytes indicative of the disturbance in erythropoiesis, i.e., hypochromia and microcytosis, anisocytosis and poikilocytosis. This is clearly an anemia of decreased production with decreased reticulocytes and decreased hemoglobin synthesis. While deficiencies may exist in the fixed tissues of the body before, or coincidental with, anemia,‖ alterations including spoon nails, glossitis, angular stomatitis and esophageal adhesions (Plummer-Vinson's syndrome, sideropenic dysphagia) usually occur only with long standing iron depletion.

* The term "iron reserve" is used to include both soluble (ferritin) and insoluble (hemosiderin) storage iron within the cell which is available for hemoglobin synthesis. Recent studies‖ indicate that these are functionally similar and probably represent the same molecular species.

† It may be assumed that iron reserves and therefore the incidence of iron deficiency anemia will be greatly influenced by iron content of the diet. Thus in certain geographic areas, i.e., England and Scandinavia, iron deficiency has been prevalent while it is quite rare in certain parts of Africa.
Fig. 1.—Iron depletion in man. Iron stores are first exhausted in the asymptomatic phase of iron depletion at which time only marrow examination will reveal iron depletion. Following exhaustion of stores, serum iron will fall, and anemia will appear. Microcytosis and hypochromia are evident several months later. Tissue manifestations (spoon nails, glossitis) indicate long standing iron deficiency.

LABORATORY DIAGNOSIS OF IRON DEFICIENCY ANEMIA

The differential diagnosis of anemia in the laboratory begins with the examination of the blood smear and the determination of erythrocyte indices (mean cell volume and cell hemoglobin concentration). In iron deficiency there may be found either hypochromia and microcytosis indicative of long standing depletion or normocytic normochromic erythrocytes following recent blood loss. Decreased blood production is indicated by the reduction in absolute number of reticulocytes* and by the normal or decreased bilirubin and fecal urobilinogen. In severe iron deficiency anemia, nucleated erythrocytes may be seen in the peripheral blood probably associated with myeloid metaplasia, but reticulocytes remain reduced. The smear in chronic iron deficiency anemia may be confused with that found in thalassemia, chronic infection, in S (sickle cell) and C hemoglobinopathies, and in marrow dyspoiesis associated with rapid maturation of erythrocytes.21 The more specific diagnostic findings relating to iron depletion are the absence of narrow hemosiderin, the absence of iron granules in the normoblast, and a low serum iron.

Attention has been directed to depletion of iron stores as the earliest phase of iron deficiency.17 These stores may be evaluated by examination of particles of aspirated marrow wherein hemosiderin granules are clearly visible (fig. 2). Considerable experience with this technic indicates that iron deficiency anemia

* The absolute reticulocyte count may be calculated from:

\[ \text{patient reticulocytes/100 rbc} \times \text{patient rbc/cu. mm.} \]

It is a useful quantitative index of the rate of blood production. When this figure is divided by the normal absolute reticulocyte count (65,000/cu.mm) values of 2 to 3 usually represent blood production of twice normal and 3 to 5 of three times normal.21
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Fig. 2
occurs for practical purposes only after tissue hemosiderin has disappeared.*

In our hands this has proved the most sensitive and reliable index of iron depletion. The appearance of the marrow in the iron deficient, the normal, and the individual with excess tissue iron is illustrated in figure 2. It is often difficult to evaluate the importance of iron deficiency in limiting erythropoiesis in anemia associated with recent bleeding. An absolute increase in reticulocytes generally means that there is some tissue iron available. Here, and in patients who have anemia of multiple etiologies, marrow examination is often essential to evaluate the possibility of iron deficiency.

**Oral Iron Therapy**

The object of therapy is to provide iron in an available form and in adequate amounts to correct the deficiency. The prescription of multiple remedies or "supplements" with iron is to be condemned. These supplements do not improve hematologic response and they are an additional expense, but more important they may obscure the diagnosis. The physician needs the knowledge that the hematologic response was to iron and iron alone; he may then continue with confidence in his more important task—to discover the reason for the iron deficiency.

The availability of ingested iron is related to its solubility and its reduced state. Ferrous salts are considered to have an absorption of 10 to 15 per cent in the usual therapeutic doses given to the anemic and iron deficient patient, in contrast to an absorption of 1.5 to 3 per cent for ferric and ammonium citrate, and 0.5 to 1 per cent for ferrum reductum. Since ferrous salts have proved effective at low dosage, they enjoy wide usage. In the adult, a therapeutic dose of ferrous sulfate (0.2 Gm. tablets) or ferrous gluconate (0.3 Gm. tablets) is one or two tablets three times daily after meals (a total daily dose of 220 to 440 mg. iron).

An elixir of ferrous sulfate is recommended for infants and small children. The usual therapeutic dose is 4 ml. three times daily representing 110 mg. of iron. For children above six or for adults, twice this dose is employed. The amount of

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* With brisk hemorrhage, a relative iron deficiency may exist with retarded hematopoiesis, and yet the marrow may contain occasional large hemosiderin granules not yet assimilated.

† While absorption of iron is 1 to 4 times greater fasting than in a postprandial state, gastrointestinal symptoms are likewise more prevalent.

**Fig. 2.**—Sternal marrow hemosiderin

a. Marrow showing no iron (Grade 0). This was aspirated from an iron deficient patient (oil immersion, unstained).

b. Marrow showing normal iron (Grade 1-2). This was aspirated from a normal subject (oil immersion, unstained).

c. Marrow showing slightly increased iron (Grade 4). This was aspirated from a patient with chronic infection (oil immersion, unstained).

d. Marrow showing marked increase in iron (Grade 5). This was aspirated from a patient with hemolytic anemia.

e. Marrow from iron deficient patient before injection of saccharated iron (oil immersion, prussian blue stain). There is no stainable iron present.

f. Marrow from the same iron deficient patient 8 hours after intravenous injection of 500 mg. saccharated iron. Blue staining hemosiderin deposits are clearly visible.
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iron given is a compromise between the local symptoms of intolerance from large doses and the slower response at low levels of iron intake. As the amount of iron is increased, the per cent absorbed progressively decreases, while the absolute amount absorbed increases. Increment effects on rate of blood regeneration with doses of over 0.4 Gm. per day of ferrous iron are, however, relatively slight. An intake in excess of 0.4 Gm. need be employed only when continued brisk blood loss or relatively poor absorption renders the response to the usual dosage inadequate.

Ascorbic acid is the one substance shown to greatly increase iron absorption through its capacity to maintain iron in the reduced state. Although the effective oral dose of iron could be reduced if combined with one gram of ascorbic acid, this has little practical value in view of the efficacy of iron alone. While it has been suggested that cobalt may accelerate the response of the iron deficient patient to iron, this has not been as yet adequately studied and cannot be recommended in view of the possible toxicity of cobalt.

Intolerance to oral iron is often avoided by starting therapy gradually. If symptoms do occur, they may sometimes be overcome by changing preparations, although there does not appear to be any particular merit of one preparation over another. Toxicity is not a serious matter. Although a number of fatalities have been reported in children from the accidental ingestion of large amounts of iron, the fifty-fold margin between therapeutic and lethal dosage makes iron one of the safest of remedies. Symptoms of nausea, vomiting, abdominal discomfort, diarrhea, constipation, pruritis ani, and inflamed hemorrhoids from iron therapy are of importance not because they lead to serious sequelae, but because they influence the patient to discontinue therapy.

The result of adequate therapy is a highly predictable one. In the iron deficient patient some 20 to 60 mg. of iron is absorbed daily, allowing the rate of red cell production to accelerate from a subnormal level to about twice normal. A reticulocytosis of 2 to 20 per cent depending on the severity of the anemia (corresponding to an absolute increase in reticulocytes of about three times normal) appears on the fifth to tenth day. The hemoglobin after a lag of three to five days rises at a rate of 0.15 Gm. a day (0.1 to 0.25) until near normal values are attained. Since reticulocytosis may be slight, it is usually more appropriate to determine the effectiveness of therapy from the rise in hemoglobin. A "significant response" must be evaluated in the light of physiologic fluctuations and error in hemoglobinometry. It is here defined as an increase in hemoglobin of 2 Gm. per 100 ml. blood or more (a rise in hematocrit of over 5). If response does not occur within three weeks, there is no reason to continue iron further. Rather, an explanation for failure should be sought.

The most likely reasons for failure in response are (1) incorrect diagnosis, (2) complicating disease inhibiting response, i.e., infection or uremia, (3) concurrent blood loss in excess of that compensated for by iron absorbed, (4) medication not taken by patient, and (5) failure of absorption of ingested iron. It should be emphasized that while impaired absorption of dietary iron may play a significant role in limiting body iron over many years, very few patients will fail to respond to iron salts. The majority of patients resistant to oral iron therapy have a widespread absorptive defect, i.e., sprue.
One limitation of oral therapy of iron deficiency anemia should be kept in mind; therapy is directed specifically at the anemia. While blood values return rapidly to normal, many months of iron therapy are required to reconstitute tissue iron stores. Accordingly, oral iron therapy must be regarded as partial replacement with the realization that the patient remains iron depleted and therefore vulnerable to future blood loss anemia.

Parenteral Iron Therapy

Indications for parenteral administration of iron in the order of their importance are:

1. Intolerance of oral iron. This is considered a valid indication only when there has been intolerance to several different regimens of oral therapy, and when the patient would prefer to remain anemic rather than take further medication due to the gastrointestinal symptoms produced.

2. Gastrointestinal disease which may be adversely affected by oral iron, i.e., regional enteritis, ulcerative colitis, or gastric ulceration. While the lesion itself may not be directly affected by iron, the disturbed physiology attending iron intolerance may activate the disease process. Here oral iron is undesirable if it produces symptoms or if the possible aggravation of symptoms is deemed too hazardous to risk.

3. Creation of iron stores. Oral iron, while effective in treating anemia, does not, as usually administered, reconstitute iron stores. In this connection, it is of interest to note the frequency of recurrence of iron deficiency anemia in the same individual. This may be attributed in part to the fact that once stores are depleted, the patient is more vulnerable to future blood loss anemia. In those patients who may expect future bleeding, i.e., in hemorrhagic diathesis or in patients with varices of the esophagus or peptic ulcer, the creation of iron stores by injection provides protection against the development of anemia.

4. Poor absorption of iron. This is exceedingly rare and usually there is some other explanation for lack of response to oral iron. There are, however, in the literature at least 39 case reports in which hematologic response followed parenteral iron after oral iron therapy was ineffective. Such patients should be carefully studied for other defects in absorption, since the sprue syndrome is usually present.

These indications express an obvious need for an effective parenteral iron preparation. To be of practical value, such a preparation should permit the injection of a hundred or more milligrams of iron without serious toxic manifestations. Ionizable iron salts injected intramuscularly in small amounts produce local discomfort and injected intravenously are extremely toxic if in excess of the binding capacity of the plasma protein. Iron replacement may be accomplished through blood transfusion. 250 ml. erythrocytes contain 275 mg. of iron and this iron will enter the body iron pool following the breakdown of the red cells. However, transfusion carries a definite risk and obscures the diagnosis since response to specific therapy is by-passed. Recently several colloidal iron preparations have been described which permit the intravenous injection of therapeutically useful amounts of iron. These include the saccharated oxide of iron, a high molecular carbohydrate iron complex, an iron-lecithin complex,
ferronicotinamide compound, and sodium dihydroxydimethylbutyrateferrate. Since the widest experience has accumulated regarding the use of saccharated oxide of iron, this material will be described in detail. Undoubtedly the remarks will apply equally well to other colloidal iron preparations of equal stability.

Saccharated oxide of iron is a negatively charged colloidal solution of iron oxide, stabilized by the adsorption of alkali and sugar. Its behavior after intravenous injection in man is illustrated in figures 3 and 4. In amounts of 50 to 200 mg, it is cleared from the serum at an exponential rate over 12 to 24 hours. Coincidental with the disappearance of iron from the serum, hemosiderin appears in the reticuloendothelial cells (fig. 2), and sucrose appears in the urine. With small amounts of injected iron, the unsaturated iron binding capacity of the serum is only slightly decreased, but with larger doses, complete saturation may be reached. Only 2 to 5 per cent of the injected dose is excreted in the urine. A typical hematologic response to a single injection of 500 mg of saccharated iron (Feojectin) is illustrated in figure 4. The response varies from oral therapy in that the reticulocyte response is greater (average absolute reticulocytes in our series increased to 5.5 times normal), indicating a greater amount of iron initially available to the marrow. The rate of hematopoiesis increases to as much as 2 to 3 times normal. Hemoglobin, after a latent period of 3 to 5 days increases at the rate of 0.22 Gm. (0.1 to 0.3) per 100 ml. a day.

In figure 5 the response of a group of iron deficient patients studied by us is illustrated. All uncomplicated patients responded with a rate of increase of hemoglobin in excess of 2 Gm. in three weeks, the average being 3.5 Gm. Subtracting a period of latency of 4 to 5 days, this coincides with a rate of 0.22 Gm. a day during response. This rate is little faster than that following oral iron. The similarity of recovery rate in anemic twins, one given oral iron and the other parenteral iron, is shown in figure 6.

The medical literature contains the results of several thousand injections of saccharated iron in over 600 patients. Various formulas have been employed to calculate total dose requirements. In our opinion dosage is satisfactorily estimated from the following considerations: the iron deficient individual needs replacement of both red cell deficit and stores to return him to true normality. In the adult the red cell deficit lies between 300 and 2000 mg. of iron depending on the severity of the anemia, and iron stores represent 1000 to 1500 mg. Total deficit is therefore between 1500 and 3500 in the 70 Kg. adult. Deficits in infants, children and adults of smaller stature are proportionately smaller and may be visualized in figure 7. Suggested therapy consists first of a trial course of injections to total 500 mg. in the adult, 250 in the child and 100 in the infant. A reticulocyte response or a rise of 2 Gm. of hemoglobin in three weeks is taken as confirmation of the diagnosis, (provided other changes in the patient’s condition such as recovery from an infection do not explain the hematologic improvement), and full replacement therapy is then given.

In the adult a single injection of iron, usually in a concentration of 20 mg. per ml., should be given over three to five minutes. The initial dose should not exceed

* The saccharated iron (Feojectin) employed in these studies was kindly supplied by Smith, Kline and French Laboratories.
Fig. 3.—Intravenous injection of 500 mg. saccharated oxide of iron (Feojectin): its immediate disposal. At 30 minutes, over 4000 μg. per 100 ml. of saccharated iron was present in the plasma. At this time transferrin (the iron binding protein of the serum) was still partially unsaturated, although between the 6th and 12th hour it became saturated with iron. Over 90 per cent of the sucrose was excreted in the first 12 hours. Coincidentally with the excretion of sucrose iron staining granules of hemosiderin were visible in the marrow (fig. 2, e and f).

Fig. 4.—Intravenous injection of 500 mg. of saccharated oxide of iron (Feojectin): its use for hemoglobin synthesis. Over the first 24 hours the injected iron is largely localized in reticuloendothelial tissue. Thereafter it is routed to the marrow and incorporated into new erythrocytes. This is illustrated in the hematologic response in one patient.
Fig. 5.—Response of iron deficient patients to intravenous iron. 1000 mg. saccharated iron (Ferojectin) was given to each patient in multiple injections. No significant response in hemoglobin occurred before 3rd–5th days after therapy was started. Thereafter, increase in hemoglobin averaged 0.23 Gm per day. This response was not greatly influenced by severity of anemia; with hemoglobin of less than 7 Gm. there was a response of 0.25 Gm. per day, over 9 Gm. 0.20 Gm. per day. Response of infants and children exceeded that of adults. (The one patient not responding was iron depleted and bleeding from a carcinoma of the sigmoid colon).

Fig. 6.—Response of identical twins with iron deficiency anemia to iron therapy. One infant received oral iron, the second received saccharated oxide of iron intravenously. There was an identical hematologic response.

50 mg., the second injection 100, and the third 200 mg. If no symptoms of intolerance have occurred, the latter dose may be given as often as once each 24 hours until the total calculated course of therapy has been completed. In infants and children 20 mg. may be given as an initial dose followed by injections of 50 mg. if the first is well tolerated.

The reported incidence of reactions has varied from 5 to 35 per cent.
Fig. 7.—Diagram of iron requirements in anemia. Attention is given only to the red cell mass and to iron stores. These increase from 200–300 mg. at birth to about 3500 mg. at 20 years. Deficit would depend on the severity of anemia. Thus a patient at 10 years with a hematocrit of 20 might be expected to have a deficit of 500 mg. in iron stores and 600 in red cell iron, a total of 1100 mg. In the adult the deficit will vary with body size but within a range of 1000 to 4000 mg. iron.

Reactions are less prominent in iron deficient patients, evidence that an increased iron binding capacity of the plasma is protective. Serious reactions have occurred with large doses of iron, and one fatality has been reported, but danger other than subjective discomfort is considered negligible within the dosage limits outlined above. Reactions of the same type are often repetitive in the same patient. A summary of reported reaction follows:

A. Local—vein spasm, extensive diffusion of iron saccharate into tissues when injected under pressure, focal extravasation due to improper venipuncture.

B. General—(1) Mild reactions: flushing of face, weakness, lightheadedness, mild headache, drowsiness; (2) Moderate reactions: general muscle soreness, severe lumbar back pain, abdominal cramps, nausea and vomiting, diarrhea, severe headache, vertigo, lacrimation, chills and fever; (3) Severe reactions: dyspnea, coughing, oppressive chest pain, tachycardia, sweating, syncope, shock with cold extremities and low blood pressure (associated with marked orthostatic hypotension). These reactions usually occur at once although some may be delayed in onset for as long as 6 to 8 hours. In the dosage recommended above, they are rarely sufficient to discourage further therapy. At the same time, they are sufficient to make promiscuous therapy the more undesirable.

Chronic toxicity from iron loading in the form of hemochromatosis is a consideration with any effective parenteral iron preparation. There is considerable evidence that large amounts of iron administered as blood transfusions may lead to iron storage disease indistinguishable pathologically from idiopathic hemochromatosis. Experimentally it has been possible to produce hepatomegaly and liver failure with ascites in dogs several years after the injection of 2 to 3 grams per kilo of iron as the saccharated oxide. These doses are far in excess of any which would be employed clinically. A toxic amount of tissue iron is con-
considered by us to be in excess of 25 Gm. Since there is no reason in man to exceed 5 Gm. of saccharated iron in any one course of therapy, the hazard is negligible. If depletion of iron stores is verified by marrow examination before further iron therapy is given, there will be no hazard from accumulation of iron during multiple courses of parenteral therapy.

**Summary**

In the normal individual the amount of iron absorbed and lost from the body each day is exceedingly small. There are certain periods during life when body iron requirements are increased; the most important of these is infancy. Here, existing iron stores are rapidly depleted, and a deficient diet can soon produce iron deficiency. Once a full complement of body iron has been accrued, the adult is independent of iron intake and becomes iron deficient only through blood loss.

In the production of iron deficiency, iron stores are exhausted before anemia appears. If any question in diagnosis from usual laboratory tests exists, the direct examination of marrow for hemosiderin will establish the diagnosis. It is of obvious importance to confirm the diagnosis by specific therapy and to determine the cause of the iron depletion.

Response to oral iron is highly predictable and failure of response usually indicates a mistaken diagnosis. In a small but significant group of patients, either unable to take iron because of gastrointestinal symptoms, unable to absorb iron, or in need of iron reserves, parenteral administration of iron has distinct advantages. The saccharated oxide of iron is an effective preparation for this purpose.

**Summario in Interlingua**

In le individuo normal, le quantitate de ferro absorbite e perdite per le corpore cata die es extrememente parve. Il ha certe periodos in le curso del vita quando le requimentos de ferro es augmentate. Le plus importante tal periodo es le prime infanzia. A iste etate le existente reservas de ferro es rapidemente exhauribile; un dieta deficientie in ferro pote rapidemente resultar in deficientia de ferro in le corpore. Post que un complete reservoir de ferro ha essite accumulare in le corpore, le individuo adulte es independent de ingestion de ferro e suffre de deficientia de ferro soimmente in consequentia de perdita de sanguine.

In le processo del production de deficientia de ferro, le reservas de ferro ex exhaurite ante le apparition de anemia. Si un diagnose inequivoc non resulta del usual probas laboratorial, le directe examine del medulla pro hemosiderina pote servir a stabilire le diagnose. Il es evidentemente de importanti verificar le diagnose per un specific therapia e determinar le causa del depletion de ferro.

Le responsa al administration oral de ferro es altemente predicibile, e le absentia del expectate responsa indica generalmente un diagnose erronee. Le administration parenteral de ferro ha distincte avantages in un parve sed significative gruppo de patientes que consiste de (1) individuos incapace a prender ferro a causa de symptomas gastrointestinal, (2) de individuos incapace a absorber ferro, e (3) de patientes qui indige reservas de ferro. In iste casos, le saccharate oxydo de ferro es un efficace preparato.
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