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Physiology and pharmacology of iron-dextran (Imferon)

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THE PHYSIOLOGY AND PHARMACOLOGY
OF
IRON-DEXTRAN (IMFERON)R

By
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A THESIS
Presented to the Faculty of
The College of Medicine in the University of Nebraska
In Partial Fulfillment of Requirements
For the Degree of Doctor of Medicine

Under the Supervision of Robert H. Messer, M.D.

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INTRODUCTION AND PURPOSE

Iron deficiency states are frequently encountered in clinical practice. All aspects of the situation have been studied for years. Nevertheless, even some of the fundamental knowledge about iron metabolism is in dispute or has undergone revision in the recent past.1,2 With such a fluctuating body of knowledge, it is not difficult to understand why the commercial market has been flooded with a variety of iron preparations each purporting to have advantages either in efficacy or in a lower incidence of toxicity. The purpose of this paper, after a brief review of iron metabolism and history of iron therapy, is to present a more detailed analysis of one of the most interesting preparations---Iron-Dextran (Imferon)R.

IRON METABOLISM

A comprehensive review of the many facets of iron metabolism will not be attempted here. Many excellent reviews and books on the subject have been published in the recent past.1,2,3,4,5 Certain disorders can cause pathological changes in ferrokinetics and iron storage, i.e., pulmonary hemosiderosis, intravascular hemolysis, Laennec's cirrhosis, etc., without affecting total body iron content to any great extent.1 However, the most frequently encountered abnormalities related to iron metabolism are related to either an excess or deficiency of total body iron. Thus, any discussion of iron metabolism must focus on factors relating to accumulation and excretion of iron by the body. (Fig. 1)

Iron excretion---

As a metabolite, iron is somewhat unique in that the excretory route is greatly limited. This feature of its metabolism has such important implications with regard to the clinical use of iron, particularly
parenteral iron, that it will be dealt with first.

In humans, approximately one-third of body iron excretion occurs in the feces and two-thirds is lost from the skin. Very little iron is excreted normally in the urine (less than 0.1 mg. per day). Urinary iron loss following parenteral iron therapy is of some interest and will be discussed later.

In the past it was felt that the colon could actively excrete excess iron. Balance studies as long ago as 1938 indicated that the body has no inherent capacity to excrete excess iron into the gastrointestinal tract. Radioisotope studies indicate that most of the iron found in the feces represents only unabsorbed iron from the diet. Total fecal iron loss including that from microscopic blood loss and desquamated intestinal mucosal cells in normal adult human subjects has been calculated at approximately 0.4 mg/day.

Total daily iron excretion is not completely fixed. Most cells contain iron somewhat in proportion to the quantity of iron in body stores. This provides for a limited selective excretion of iron in daily obligatory loss of cells and secretions. For example, after blood transfusions have caused excessive iron stores, excretion of iron exceeds absorption by about 4 mg. per day in an effort to reestablish normal body iron equilibrium.

Normal daily excretion in the human male probably does not exceed 1 to 2 mg. per day. In the female, where most cases of iron-deficiency in this country are encountered, additional losses are incurred through menstruation, pregnancy, and lactation. In the menstruating female, an additional 0.3 to 1 mg. per day is required. Pregnancy demands another 2 mg. per day for the duration of gestation and lactation.
The total extra iron loss to the mother is at least 500 mg, attributed to the fetus, placenta, and blood loss at delivery. 6,7

Except for the increased loss of iron in females as noted above, the restricted loss of iron from the body is explained by the intracellular location of most of the iron either in tissue stores of incorporated in hemoglobin and by the tight chelation by transferrin of that small fraction in transit through the plasma. (Fig. 1)

It is important to know whether parenterally injected iron compounds influence the normal excretion of iron. This will be discussed later.

Iron absorption---

Iron absorption from the gastrointestinal tract is regulated by factors in three anatomic locations. Intraluminal factors include anatomic abnormalities, dietary constituents, and intestinal secretions. 1,2,4 (Table 1)

Interest in mucosal cell factors has centered around the presence or absence of a "mucosal block" initially proposed by Granick. 8 According to this theory, iron absorption was regulated by an iron-accepting protein of the intestinal mucosal cell called apoferritin. However, recent work causes some objections to this theory. 3 It is now felt that iron either in ionic form or in a low molecular weight complex crosses the mucosal cell to the vascular border, where it is transferred to the plasma by an oxidative process which appears to be the rate limiting reaction. Iron that is not rapidly transferred to plasma is complexed with apoferritin to form ferritin, a form of storage iron. In this concept, the apoferritin has no direct regulating affect on iron absorption.

The third anatomic location exerting some regulatory influence on iron absorption from the gut is corporeal with reference especially to the demands of erythropoiesis and the tissue iron stores.
The factors regulating iron absorption are very complex and our understanding of their interrelationships is somewhat less than complete.

Iron transport--

At any one time there is normally only about 3-4 mg. of iron in the plasma. Most of the iron entering the plasma is derived from the reticuloendothelial system following breakdown of hemoglobin and the major portion leaving the plasma is directed to the bone marrow for hemoglobin synthesis. Iron released from tissue stores, tissue enzymes, and the gut also contributes to the plasma iron pool, although to a much lesser extent. In the plasma it is bound to a protein called transferrin which is made in the liver and has the electrophoretic mobility of a Beta-1 globulin. It is normally present in the plasma in a concentration sufficient to bind 280-400 mcg. of iron per 100 ml. of plasma. Normally only one-third of the transferrin is bound to iron.

Iron storage--

Storage iron in the normal adult comprises about 20-25 per cent of the total body iron. Phlebotomy studies by Pritchard revealed the average iron stores in normal adult males to be 819 mg. while those in normal nulliparous women were only 254 mg.

During the course of normal pregnancy there is an increase in red blood cell volume and plasma volume. The latter is greater than the former so "hydremia" develops with a decreased red blood cell count and hemoglobin concentration. The majority of workers consider this finding as physiological. Others have presented evidence that adequate iron stores will almost completely prevent this occurrence. They point out that the Bantu Negroes in South Africa, who display
tissue siderosis resulting from excessive dietary iron, rarely have a decrease in hemoglobin concentration during pregnancy.

Iron stores exist as an intracellular iron-protein complex in two different forms. Normally the largest portion is stored as ferritin (60 to 70 per cent) which is water soluble and cannot be demonstrated by staining methods for iron. The rest of the iron is stored as hemosiderin which is water insoluble, stainable and thought to be less readily available than ferritin. In cases of microcytic, hypochromic anemias examination of marrow for hemosiderin has proved to be a reliable method for evaluating iron stores and establishing a diagnosis of iron-deficiency anemia.

Most of the ferritin in the body is located in the reticuloendothelial and parenchymal cells of the liver and spleen. During iron overload other parenchymal cells contain significant quantities of iron. (This will be discussed further in a later section.)

Ferrokinetics---

Radioisotopic methods have added greatly to our knowledge of iron metabolism. Such studies have allowed us to measure iron turnover rates and to appreciate the relative importance and dynamic status of the various metabolic circuits.

The half time of plasma clearance of iron is 60 to 120 minutes and the total iron turnover is 20 to 40 mg. per day. In the normal adult male about 21 mg. of iron per day is utilized and released by hemoglobin metabolism. (Fig. 1) Actual human ferrokinetics are more complex than is indicated by the brief description above. An integro-differential mathematical analysis of the data indicates that there are both slow and fast components of iron leaving and entering the plasma.
REVIEWS OF HISTORY OF PARENTERAL IRON THERAPY

The efficacy of oral iron therapy in iron-deficiency anemia has been well substantiated in the literature. Most workers have found that in the majority of cases the rate of hemoglobin regeneration is nearly the same using either oral or parenteral iron preparations. Some workers, however, have reported that the rise in hemoglobin after parenteral iron is "double" that of the orally treated patients. After the hemoglobin mass has returned to normal with oral iron therapy, several more months of continuous iron therapy are required to bring about full restoration of the depleted iron stores. There are other problems with oral iron therapy. In one study on the effects of iron on pregnant women gastrointestinal side effects such as constipation, nausea, abdominal pain and diarrhea occurred in almost 20 per cent of patients. However, only about 1 per cent of the patients in the above study could not tolerate oral iron in any form. These problems with oral iron have led investigators to search for an iron preparation suitable for parenteral administration. (Other specific indications for parenteral iron therapy will be discussed later.)

Attempts to supply iron parenterally were made as early as the late nineteenth century. Iron citrate and ferrous gluconate were tried subcutaneously and intramuscularly. The earliest intravenous preparations were colloidal ferric hydroxide and colloidal ferric oxide. All these compounds proved to be too toxic because they liberated ionic iron into the plasma too rapidly. The free iron exceeded the iron-binding capacity of transferrin leading to such toxic symptoms and signs as a feeling of general warmth, palpitations, flushing of the face, engorgement of the neck veins, nausea, vomiting, and even vascular
The first practical parenteral iron preparation was introduced in 1947. It was a saccharated iron oxide compound administered intravenously. Early studies with radioiron showed that iron injected intravenously is rapidly utilized for hemoglobin production. However, even with this substance a significant number of severe toxic reactions occurred.

The search continued for a compound which would complex the ionic iron securely enough to prevent toxicity and yet release it readily for hemoglobin production. In 1954 a new iron compound was introduced. It was an iron-dextran complex which was found to be extremely well tolerated in mice following large doses either intramuscularly or intravenously.

Since its introduction this preparation has been the subject of a great deal of controversy. It was even withdrawn from the market for a short time in 1960 following reports that it had a carcinogenic potential.

IRON-DEXTRAN (IMFERON)

Preparation and chemical properties

Dextran with molecular weight of 2000 to 20,000 is dissolved with anhydrous sodium carbonate in hot water. Ferric chloride is added after the solution is cooled. Carbon dioxide is liberated and the resultant solution contains colloidal ferric hydroxide with low molecular weight dextran. After concentration it contains 5 per cent iron and has a pH of 5.2 to 6.0. The sodium chloride content is 0.9 per cent. The complex is weakly negatively charged, isotonic with tissue fluid and will not precipitate in plasma over a very wide pH range.
The commercial preparation contains 50 mg. of elemental iron per cc.

Pharmacology---

1. Absorption

The route and rate of absorption following intramuscular injection depend on the molecular size and local effect of the injected substance. Substances of molecular weight 20,000 or more are absorbed almost exclusively by the lymphatics while those under 5,000 enter the blood stream primarily. The average molecular weight of the dextran used in the manufacture of iron-dextran complex is 5,000, but the final molecular weight of the complex is many times this figure. Following Fe$^{59}$ labelled iron-dextran injection, there is no activity or rise in serum iron for 4 to 6 hours. However, stainable iron is found in the regional lymph nodes within an hour of injection. Thus, it appears that iron-dextran is removed from the site of injection by the lymphatic system.

About 80 to 90 per cent of an injected dose is absorbed in 48 to 72 hours with very slow absorption of the remaining material. In rabbits 98 per cent of a large intramuscular dose was absorbed after 42 days. Lymphatic absorption is dependent upon the rate of lymph flow and upon lymphatic capillary permeability both of which are increased in an acute inflammatory reaction. Histological studies have shown an acute inflammatory reaction with degenerative changes in the muscle fibers at the site of injection. This inflammatory focus would be expected to enhance absorption of iron-dextran. Within 24 hours tissue macrophages begin to appear at the injection site and show a positive stain for iron. It is interesting that the number of these iron-containing macrophages remains undiminished for as long as three months.
It is apparent that iron-dextran uptake by local macrophages makes the iron no longer immediately available to the metabolically active iron pool. This macrophage uptake explains the slow absorption after 72 hours. Recent studies using radioiron tagged iron-dextran have shown that the last of multiple daily injections is consistently better absorbed than a single injection. It would appear that the initial injection opens up the lymphatic drainage channels so that they are already working efficiently when subsequent injections are given.

2. Serum iron

In cases of acute iron poisoning, shock or coma has been reported in 37 per cent of patients whose initial serum iron levels were 500 mcg. per cent or more. In patients treated with daily intramuscular injections of 250 mg. of iron-dextran the serum iron content rose to an average of 1100 to 1200 mcg. per 100 ml. on the third to fifth day with no evidence of toxic symptoms. This indicates that the iron is not in the ionized state but is still complexed with dextran. The iron-binding capacity does not decrease, i.e., become more saturated with ionized iron, until about 72 hours after intramuscular injection. The serum iron content usually returns to normal values within two to three weeks after intramuscular injection. It is of interest that serum iron levels of 104,000 mcg. per 100 ml. have been reported following intravenous infusion of iron-dextran without toxicity.

3. Urinary excretion

Due to the high molecular weight of the complex one would not expect urinary loss to be significant. Studies with radioiron support this assumption in that less than 0.2 per cent of an intravenous dose is lost in the urine in the first 72 hours following infusion.
levels of urinary iron excretion have been reported in rabbits following high doses of intramuscular iron-dextran. 28 However, this excretion occurred only at doses in excess of 600 mg. Fe per kg. body weight and did not occur at dosage levels approximating those used in clinical practice, i.e., about 20 mg. Fe per kg.

4. Metabolism

It is evident from the preceding discussion that the iron-dextran complex is very stable in the plasma. However, in order for iron to be utilized for hemoglobin synthesis it must be in an ionized state. Therefore, the dextran moiety must be readily split off from the iron in order for it to be an effective hematinic. The reticuloendothelial system would be the logical place for such degradation and, indeed, several good studies have confirmed this assumption. 9,23,25,27 As discussed previously, the reticuloendothelial system is important in internal iron turnover:

(a) It removes hemoglobin or non-viable erythrocytes from the circulation.

(b) It splits off the iron from the heme moiety.

(c) It returns iron to the plasma for transport to the marrow.

(d) It serves as a potential reservoir for storage iron.

Noyes et al.9 infused radioiron-tagged erythrocytes into rabbits and humans. They found an almost immediate increase in surface counting over the liver and spleen. They found radioiron bound to transferrin within thirty minutes after injection of the tagged red cells indicating rapid processing by the reticuloendothelial system. Using larger
quantities of tagged red cells, they discovered that considerable
amounts of iron were retained in the reticuloendothelial system for
twelve days prior to its release into the plasma. Ingestion or
parenteral injection of iron did not cause an increased release of iron.
The only stimulus to increase the release of iron from the reticulo-
endothelial system was a state of increased erythropoietic activity.

Surface counting in more recent studies using radioiron-tagged
iron-dextran have shown similar increases over liver and spleen. Following intravenous infusion the tagged complex had a half-life of
2.5 to 3 days and the plasma was completely cleared in 10 days. It
should be noted that surface-counting patterns are similar after either
intravenous or intramuscular administration of the complex. In either case the peak radioactivity is reached about day 7 with the
splenic rise being less marked than that of the liver. In anemic sub-
jects, there is a gradual decrease in hepatic and splenic counts over
the next 14 days. These patterns suggest that the liver and spleen are
the main initial storage sites of the iron-dextran complex, and that
the iron is gradually split off to subsequently appear in hemoglobin
in the circulating erythrocytes.

There is evidence to suggest that the liver and spleen handle iron
differently. It is felt that iron is rapidly released by the spleen
for transport to the marrow, while liver iron is held in more slowly mov-
ing stores. It has been found that the plasma clearance of iron-dextran
is related to the availability of apoferritin needed to form the storage
compound called ferritin. Studies on the influence of the type of
iron compound administered on the distribution of storage iron between
ferritin and hemosiderin revealed some marked differences in distribution.
Under conditions of iron loading, rabbits receiving saccharated iron oxide showed a marked increase in hemosiderin deposition while rabbits receiving iron-dextran showed a more marked increase in ferritin formation. This difference in distribution may be the result of differences in the rate at which iron is released from the complexes. Saccharated iron oxide is cleared from the blood within 24 hours while iron-dextran requires 72 hours or more. Perhaps the slower degradation of iron-dextran allows the liver time to synthesize sufficient apoferritin to keep up with the liberated iron.

Regarding ferritin formation, there is a similarity between iron-dextran and ferrous sulfate. Both compounds have high magnetic susceptibilities as determined by their magnetic moments while saccharated iron oxide and ferric hydroxide with slower ferritin production have lower magnetic susceptibilities. Further studies are needed to determine whether this magnetic state is of significance in the rate of release of iron from its carrier or in the rate of its incorporation into the ferritin molecule.

5. Effect on organ system function

Almost all the studies done with iron-dextran, both experimental and clinical, have measured such parameters of organ function as BUN, standard liver function tests, testicular function tests, etc., and have uniformly reported no significant changes in function after iron-dextran. A recent study with intravenous iron-dextran investigated the effect of the therapy on blood-grouping, coagulation, sedimentation, and hemolysis. There was no change in erythrocyte sedimentation rate, blood coagulation nor was there any significant hemolysis. ABO and Rh blood grouping and cross matching were not influenced.
Since the pregnant female is frequently found to be iron-deficient, it is worthwhile to consider the placental transfer of iron and possible effects of iron-dextran therapy on the fetus. Normally the only source of fetal iron is the iron circulating in maternal plasma bound to transferrin. 30 Placental transfer of iron is an active process independent of the fetus. Fetectomy in rats does not result in a decrease in placental uptake of iron. 31 This uptake occurs against a concentration gradient and retrograde transfer from fetus to mother does not occur. The amount of iron transported increases markedly as pregnancy progresses. In the rabbit 90 per cent of plasma iron turnover is directed to the fetus at the end of pregnancy. 30,32 No information was found in the literature on the placental response to circulating iron-dextran. This would appear to be an area requiring more investigation.

Clinical efficacy

Most investigators report earlier and higher reticulocytosis, but similar responses in hematocrit and hemoglobin concentration in comparing oral with parenteral iron therapy.* Reticulocytosis may start as early as the third day and reach a peak at 5 to 10 days of 10 to 15 per cent. 15 With oral therapy the mean peak value is about one-half the above value and is not reached until 6 to 16 days following institution of therapy. The magnitude of response to iron therapy usually reported is summarized in Table 2. It should be mentioned that the rate of response depends on the severity of the anemia. In severe anemia the rate of response may exceed 2 gm per cent per week. 15 In one study of 75 anemic women treated with iron-dextran as a total dose intravenous infusion, 30 cases showed a rise in the hemoglobin value of 1 to 2 gm

References: 7, 14, 15, 16, 17, 33, 34, 35, 36, 37, 38
per cent within 48 hours. (The average hemoglobin rise in this study was 1 gm per cent per week.) This early rise, although unexpected, is possible since stainable iron is present in the marrow at 12 hours after infusion.

1. Methods of administration

At the present time the manufacturer of iron-dextran recommends that in the United States it be administered only via the intramuscular route. Many formulas for determining dosage have been suggested, all based on hemoglobin deficit, body weight and status of iron stores. Probably the easiest rule to remember is as follows: 250 mg of iron (5 ml of iron-dextran solution) for each gram per cent of hemoglobin deficiency. Dosages greater than 5 ml in each buttock per day result in appreciable muscle soreness. To prevent brown staining of the skin at the site of injection, a Z-track technique with a two or three inch needle is used. It should be remembered that 20 to 25 per cent of an intramuscular dose is not readily available for hemoglobin production because of poor absorption after the first 72 hours.

There are certain disadvantages to the intramuscular administration of iron-dextran that make the intravenous route more appealing such as: (1) patients tire of having repeated painful injections, (2) difficulty of administration in asthenic patients with little muscle mass, (3) possibility of brown staining of the skin, and (4) rare patients with idiopathic thrombocytopenic purpura or other bleeding disorders who may have severe tissue bleeding after intramuscular injections. Therefore, the total dose infusion technique was introduced in 1963. Actually the complex was found to be the least toxic of all iron preparations when given intravenously to animals as early as 1955. The LD₅₀ following
intravenous infusion in mice is over 1,000 mg of iron per kg body weight. Basu \(^{46}\) reported that work in laboratory animals has shown that iron-dextran complex, in company with physiological iron such as ferritin, has a powerful general adrenolytic effect, causing hypotension, when introduced rapidly into the blood, but this effect does not appear when the complex is diluted and given slowly. Marchasin and Wallerstein \(^{39}\) have used undiluted iron-dextran intravenously in doses up to 3000 mg in 45 patients. No serious untoward effects were observed in this study. One patient developed chills and mild abdominal cramps 8 hours after injection. However, most investigators have chosen to administer the iron-dextran diluted in 5 per cent glucose or normal saline in various concentrations, usually about 10 to 25 ml diluted to 500 cc. \(^{16,23,27,36,38,40,41}\) Most investigators report a hemoglobin rise of 1 to 2 gm per cent per week which is comparable with results in successful oral\textendash;intramuscular therapy. In order to prevent severe reactions certain precautions need to be taken into consideration before selecting patients for this form of therapy.

(a) Patients with cardiac disease should be excluded to prevent overloading the circulation and cardiac failure.

(b) It has been found that patients with active pulmonary disease have a higher incidence of bronchospasm after the intravenous administration of iron.

(c) Severe reactions have been reported in cases of toxemia of pregnancy with albuminuria so that patients with uncontrolled toxemia and kidney disease should be excluded.

(d) Severe reactions have also been reported if intravenous or intramuscular iron-dextran is followed 10 to 20
days later with a massive intravenous infusion.

(e) Normal saline has been reported to be better tolerated than 5 per cent glucose for the infusion of iron-dextran complex. 36

(f) Most workers suggest using a test dose by running the infusion very slowly for the first few minutes. If the patient complains of giddiness, chest pain, cough, or any other discomfort the infusion is discontinued.

2. Indications for parenteral iron

For the great majority of cases of iron-deficiency anemia, parenteral iron offers no advantages over oral iron therapy. However there are certain valid indications for parenteral iron and these should be enumerated.

(a) Malabsorption of iron from the gastrointestinal tract as in:

(1) Total or subtotal gastrectomy
(2) Intestinal disease such as sprue
(3) Steatorrhea

(b) Proved intolerance to oral iron.

(c) Inability to be sure that oral medication is taken as in:

(1) Inmates of institutions
(2) Children
(3) Patients from low socio-economic groups
(4) Geriatric patients

(d) Selected chronic hemorrhagic states such as congenital telangiectasia. 42
Adverse effects and toxicity

The adverse effects in 60 patients treated with intramuscular iron are summarized as follows: 34

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local discomfort---</td>
<td>All-----</td>
</tr>
<tr>
<td>Pain radiating down back of leg-</td>
<td>3--------</td>
</tr>
<tr>
<td>Brown staining of skin----------</td>
<td>5--------</td>
</tr>
<tr>
<td>Episode of giddiness and malaise for 1 hour after injection--</td>
<td>1--------</td>
</tr>
<tr>
<td>Dyspnea, paresthesias, and epigastric pain occurring 24 hours after injection--</td>
<td>1--------</td>
</tr>
</tbody>
</table>

Occasional transient allergic reactions have been reported such as urticaria, arthralgia, lymphadenopathy, nausea, vomiting, headache and fever. 33,44,45,46,47 These reactions usually respond well to supportive medication and antihistamines. An interesting finding was reported by Bowman35 in anemic children treated with intramuscular iron-dextran. In three patients with severely depressed hemoglobin levels (1.9 to 2.6 gm per cent), iron-dextran therapy resulted in a leukoerythroblastic response as noted on peripheral smear. The granulocytic leukocytosis was not unlike that of chronic granulocytic leukemia with band forms, metamyelocytes, myelocytes, occasional progranulocytes and rare myeloblasts appearing on peripheral smear. These responses were transient and
disappeared by the fourteenth day.

Studies of acute and chronic toxicity in animals have shown iron-dextran to be the least toxic of all the iron preparations. Acute toxicity findings were mentioned previously. In determining the chronic toxicity of the preparation, mice, rats, and guinea-pigs have been given total doses of more than 30 times the usual clinical dose and, more than a year later, have shown no ill-effects whatsoever.\textsuperscript{24,38} In antigenicity studies, there were no signs of anaphylaxis in guinea-pigs when the challenging dose was administered 14 days after sensitization with iron-dextran.\textsuperscript{24} In the same report no serum antibodies were produced in rabbits which would react with either dextran or iron-dextran.\textsuperscript{24}

Karlefors and Norden\textsuperscript{17} found that reactions were most common on the fourth day after the initial intramuscular injection. Since skin tests with iron-dextran were negative and complement fixation studies and precipitin reactions were equivocal, they felt that the theory of a sensitizing mechanism could not be supported. It was their opinion that most of the reactions were due to the toxic effect of ionic iron split off in the reticuloendothelial system.

Severe reactions and even several deaths following iron-dextran therapy have been reported.\textsuperscript{43,44,45,46,47} The more disturbing reactions include headache, vomiting, and fever\textsuperscript{17}, recurrent arthralgia and cellulitis\textsuperscript{43}, transient shock-like conditions\textsuperscript{44}, fever with painful enlargement of the inguinal lymph nodes\textsuperscript{45}, encephalopathy\textsuperscript{46}, joint effusion\textsuperscript{46}, and one case of cerebral hemorrhage leading to death.\textsuperscript{46} The cause of death was "ventricular hemorrhage most probably due to acute hypertension resulting from the toxic effects of iron on the kidney."\textsuperscript{46} Iron was deposited in the endothelial lining of the
capillary loops of almost all the glomeruli. Under conditions of iron loading with iron-dextran, rabbits died with kidney findings similar to the case above. One study showed that reactions were more common in pregnant women than in the non-pregnant. They also found that reactions were more common and severe when the anemia was dimorphic and when pre-eclampsia was present. The incidence of reactions did not seem to bear any relationship to the severity of anemia, the dosage of iron-dextran, and the serum protein level. It would seem likely that some of the reactions reported are allergic in nature or due to some hypersensitivity, but proof awaits further investigation.

Intensive and prolonged administration of iron parenterally in animals results in siderosis of the liver, spleen, inguinal lymph nodes, and occasionally of lymph nodes elsewhere. This was not accompanied by any detectable disturbance of liver function. Severe iron overload by itself does not appear to induce tissue damage. However, studies on iron-induced liver damage support the conclusion that a liver loaded with iron is more vulnerable to the action of toxic agents or deficient diets. After 40 weeks of iron-dextran injections in monkeys the liver was found to contain much iron in macrophages and also in parenchymal cells, but no histological evidence of cirrhosis or of any pre-cirrhotic changes was observed.

Carcinogenic potential

In 1959, Richmond reported sarcoma production at the site of injection of iron-dextran in rats. This effect has been well substantiated by others in mice and rats and is now undisputed. However, most of these studies have been done with larger doses than those used clinically in relation to body weight. In 1960, Robinson et al reported a human
case of possible association of malignant neoplasm with iron-dextran injection. Four years after a short series of iron-dextran injections in the left deltoid area of a 74 year old white female, a soft mass was noted. The initial pathological diagnosis was undifferentiated sarcoma. There was a marked difference in the histologic appearance of the tumor and those produced in rats. Since that time slides of this tumor have been sent to many pathologists in the U.S.A. and Canada. There was a great deal of variation of opinion as to the type of tumor although the majority agreed that it was malignant. Roe and Carter tested the assumption that sarcomas were produced only at very high doses. They found sarcomas at the site of injection in 8 out of 16 rats receiving 16 injections of 0.75 ml of iron-dextran at weekly intervals. In 128 rats receiving 2 injections of 0.75 ml of iron-dextran only 5 sarcomas were found. The most malignant tumors were found in animals receiving the highest doses. It should be pointed out that the animals on the lowest dosages received an amount equal to 375 mg per kg body weight which is still considerably more than the average clinical dose of 20 mg per kg. The majority of tumors appeared only after 400 to 600 days following injections. It has been suggested that the latent period before the appearance of iron-dextran sarcomas may be as long as one-quarter to one-third of the life-span of the species in question. Monkeys failed to develop tumors after as many as 40 weekly injections of 0.25 ml iron-dextran. They were observed for as long as a year, but this period of observation may still have been too short. In view of the long latent period between exposure to iron-dextran and the appearance of sarcomas we may have to wait 15 to 20 years for a useful answer to the question of possible carcinogenic effect of iron-dextran in man.
Summary and conclusions

After a brief review of iron metabolism including information from some of the newer ferrokinetic studies, the physiologic and pharmacologic effects of iron-dextran were discussed. It would appear that in the majority of cases of iron deficiency oral iron therapy is indicated because of the possible adverse effects and toxic reactions from iron-dextran. Most investigators report similar clinical responses with oral or parenteral iron therapy. Specific indications for parenteral iron therapy were discussed.

Iron deficiency in the United States is probably most common in pregnant women. A higher incidence of toxic reactions following iron-dextran therapy has been reported in pregnant than in non-pregnant women. Very little information is available on the effects of iron-dextran on the fetus and placenta. Since considerable numbers of pregnant women are receiving iron-dextran, studies on placental transfer of this substance should be done.

The total dose infusion technique introduced recently offers several advantages over intramuscular injections. Since the reported incidence of reactions seems to be no greater with this method, it deserves further investigation.

A great variety of reactions to iron-dextran have been reported. Some of these reactions are undoubtedly due to the toxic effect of ionic iron split off too rapidly by the reticuloendothelial system. Others seem to have an allergic or hypersensitivity basis. Further studies in this area seem indicated.

The question of possible carcinogenic effect of iron-dextran in man is unresolved. Since the latent period may be as long as one-third
of the life span of the species, we may have to wait 15 to 20 years for a useful answer.
Figure 1: Iron Metabolism

- Hemolysis: 0.8% R.B.C. daily
- R.B.C.: 2500 mg
- R.B.C. Production: 0.8% R.B.C. daily
- (R.E. System) 20 mg daily
- Absorption: 1 to 2 mg daily
- Plasma Pool: 4 mg
- Excretion: 1 to 2 mg daily
- 5 mg daily
- Body Stores: 1000 mg
- Myoglobin: Resp. Enzymes 300 mg

## Table 1

**Intraluminal Factors**

<table>
<thead>
<tr>
<th></th>
<th>Increase Absorption</th>
<th>Decrease Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIETARY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Precipitating chelates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. carbonate</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>b. phosphate</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>c. phytate</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>d. oxalate</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2. Sugars</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3. Amino acids</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4. Other reducing substances</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>e.g. Ascorbic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTRIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. HCl</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2. Intrinsic factor</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3. Gastroferrin</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>BILE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ascorbate</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2. Glutathione</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>PANCREAS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bicarbonate</td>
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<td>X</td>
</tr>
</tbody>
</table>
Table 2
Response to Iron Therapy

<table>
<thead>
<tr>
<th>IRON PREPARATION</th>
<th>DOSE (mg)</th>
<th>NO. OF SUBJECTS</th>
<th>INITIAL HEMOGLOBIN (gm %)</th>
<th>INCREASE PER DAY (gm %)</th>
<th>TOTAL HEMOGLOBIN PRODUCTION (X NORMAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular:</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1. Iron-Dextran</td>
<td>250</td>
<td>14</td>
<td>4.9</td>
<td>0.28</td>
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<tr>
<td>2. Iron-Sorbitex</td>
<td>100</td>
<td>11</td>
<td>4.9</td>
<td>0.26</td>
<td>2.8</td>
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<tr>
<td>Oral:</td>
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<tr>
<td>3. Ferrous Sulfate</td>
<td>180</td>
<td>10</td>
<td>5.1</td>
<td>0.25</td>
<td>2.8</td>
</tr>
<tr>
<td>4. Ferrous Gluconate</td>
<td>220</td>
<td>10</td>
<td>4.9</td>
<td>0.25</td>
<td>2.7</td>
</tr>
<tr>
<td>5. Ferrous Fumarate</td>
<td>200</td>
<td>8</td>
<td>4.9</td>
<td>0.26</td>
<td>2.9</td>
</tr>
</tbody>
</table>

BIBLIOGRAPHY

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