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Intravenous Iron Therapy

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I. INTRAVENOUS IRON THERAPY*

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1. Introduction

For many years attempts have been made to use intravenously administered iron in the treatment of hypochromic anemia. In principle the intravenous route of administration offers the most effective means of rapidly replacing deficient iron stores. In practice severe toxic reactions from the injected iron have precluded its use under other than exceptional circumstances. Recently by use of a saccharated iron oxide, the toxic symptoms have been reduced to a minimum, thus permitting easy and safe administration of relatively large intravenous doses of iron. This presentation is a preliminary report of our experiences with treatment of pregnancy iron deficiency anemias by means of intravenously administered saccharated iron oxide.

2. Historical Review

Numerous references to parenteral iron administration are present in the literature. Most reports deal with animal experiments where studies were being carried out on various aspects of iron metabolism. The effectiveness in humans of intravenously injected iron has been amply demonstrated, but as stated by Goetsch[1] (1946), "The toxic effects of parenterally administered iron were certainly severe enough to preclude its use for therapeutic purposes except under the most unusual circumstances."

Stockman[2] (1893) reviewed the available literature to that date. This author attempted to prove by parenteral administration of inorganic iron that inorganic iron was directly absorbed and utilized as such, as opposed to two other concepts of that time which held that only organic or food iron was utilized by the body. One such theory held that the inorganic iron merely "stimulated" the absorption or organic iron from the food. Another theory current for that time postulated that in the breakdown of food "toxic sulphides" were liberated which prevented the absorption of organic iron. Inorganic iron neutralized these toxic sulphides and permitted free absorption of the organic iron. Heath and Castle[3] (1932) found that 96 per cent of intravenous iron was utilized for hemoglobin synthesis but concluded that toxic reactions were too severe to warrant its clinical use. Whipple and Robscheit-Robbins[4] (1936) found in anemic dogs that colloidal ferric hydroxide was quantitatively used for hemoglobin synthesis. 10 mgm. of iron given intravenously was required to produce three grams of hemoglobin. Hahn and Whipple[5] (1936) recovered 56-70 percent of injected iron in the spleen and liver of anemic dogs. Witts[6] (1933) in a review of ideopathic hypochromic anemia concluded that parenteral iron administration was impractical owing to the pain of injection and the danger of iron poisoning. It is of interest that in this paper Witts described a small percentage of the total group of ideopathic hypochromic anemia as being refractory to orally administered iron. Goetsch and Moore[1] (1946) demonstrated the effectiveness of intravenously administered ferric hydroxide and oxide. They gave 0.6 to 1.32 gm. of these preparations in single doses to 8 individuals with hypochromic anemia and to 3 normal subjects. In the anemia cases the reticulocyte response was significantly greater than after optimal oral iron therapy. There was no reticulocyte response in any of the normal subjects. They concluded that 72-99 per cent of the injected iron was utilized for hemoglobin production. As previously mentioned they found the toxic reactions to be severe. Finch[7] (1949) by means of radioactive iron studies has demonstrated that with iron given intravenously to iron deficient subjects, the initial utilization is more rapid and complete than in the normal subject. In our own earlier studies[8] ferrous ascorbate was given intravenously. The clinical effectiveness in pregnancy anemia was shown but toxic reactions prevented the use of larger doses and venous throm-

*This study was aided by a grant from the Eli Lilly Company.

bus formation prevented its use in smaller doses over longer periods of time.

Saccharated iron oxide was used by Cappell[9,10] (1929,1930) in intravitam staining experiments. His experiences were similar to those reported by Polson[11,12] (1928,1929) who had used a dialysed iron preparation. Polson described the fate of intravenously injected iron in his animals, some of them being sacrificed 14 months after the iron injection. He described a deposition of iron in the lungs which Cappell using saccharated iron oxide did not find. The dialysed iron had in part flocculated on contact with blood with resulting pulmonary embolism. Saccharated iron oxide did not produce a flocculation with blood, consequently pulmonary embolism did not occur. This fact has been offered as one of the reasons that saccharated iron oxide is less toxic for humans. In terms of the chronic effects of intravenously injected iron, these authors found no evidence of any lesions suggestive of hemochromatosis. In one animal a liver lesion suggestive of cirrhosis was found on autopsy. In brief the injected iron was first picked up by the cells of the reticulo-endothelial system and by some leukocytes in the same way as other suspensoid substances such as carbon. Unlike carbon the injected iron was not inert and later moved into the permanent storage depots. The most important of the depot sites were the liver and spleen. It is to be noted that the pancreas was not involved in any of their animals.

Mannich and Rojahn[13] (1922) studied saccharated iron oxide and concluded that it was a negatively charged colloidal solution of iron oxyhydrate, stabilized by adsorption of alkali and sugar. Nissim[14] (1947) reported the use of saccharated iron oxide in humans. In two patients by single injection he gave 1 gram of the material with the production of only mild toxic symptoms. Seven patients with anemia were given single injections of 500 mgm. with reactions appearing in two instances. Thrombophlebitis was successfully averted in all his injections by running in 5 per cent dextrose after the iron injection. The intramuscular or subcutaneous injection of the saccharated iron oxide caused marked local reaction and pain which, however, disappeared within two hours.

Davidson and Girdwood[15] (1948) successfully treated one case of hypochromic anemia which had been refractory to oral ferrous sulfate over a long period of trial. It is of interest that this individual had not responded to Mol-Iron. 1.5 grams of saccharated iron oxide was given in small doses over 50 days. A maximum reticulocyte response of only 3.2 per cent was noted on the 10th day but the hemoglobin rose from 36 per cent to 90 per cent over this period of 50 days. Mild reactions only were noted with the last three injections. Slack and Wilkinson[16] (1949) reported their experiences in the treatment of 60 patients. Optimal single dose was 200 mgm. since larger doses such as 300 mgm. produced a high percentage of mild reactions. Fifty seven of the 60 anemias responded to the saccharated iron oxide administration. In over 800 injections only 4 veins were thrombosed. Reticulocyte responses of 10-18 per cent were observed in most of their cases. In one instance a serum iron of 3635 gamma per cent was noted immediately after injection of the iron. Govan and Scott[17] (1949) reported 25 pregnancy anemias treated with saccharated iron oxide. 3 of the 25 pregnancy anemias had not responded to oral iron therapy. The highest reticulocyte response was 16 per cent. One moderately severe reaction resembling an anaphylactoid reaction was noted. French[18] (1949) in a letter to the Lancet cited his own experience with saccharated iron oxide in general practice. In all he had used over 2 liters of the preparation and "concluded that it is a bland and reliable preparation." He noted no complication from its use.

3. Saccharated Iron Oxide

The saccharated iron oxide used in this study was generously supplied by

Sharp and Dohme, Inc. The material was prepared by essentially the same method as described by Slack and Wilkinson[16]. Sterilization was accomplished by autoclaving, first in the bulk form and later in the 10 cc. vial. The pH of the preparation under study was adjusted to 9.05. The studies of Mannich and Rojahn[13] showed the colloid at this pH to be in the sol phase and that lowering the pH resulted in conversion to a gel. This observation has been confirmed by Slack and Wilkinson[16]. The latter investigators also found that autoclaving increased the toxicity of the product. They found that sterilization by Seitz filtration gave a product which was less toxic.*

Ross, McKinney, Peck and Beyer[19] have carried out toxicity studies on the preparation used in our experiments. In general they found that saccharated iron oxide was relatively non-toxic by comparison with other pharmacologically active drugs. A mild local tissue effect was noted which they believed to be due, in part, to the alkalinity of the solution. In dogs, rabbits and rats no venous thrombus formation was observed following intravenous injection. In rats the spleen and liver were observed to be the major depots of iron storage. Little change was observed in the cardiovascular and respiratory systems on injection of saccharated iron oxide in dogs. The authors concluded that a "cautious clinical evaluation of saccharated iron oxide seemed justified."

4. Dose and Method of Administration

Our own experience has not been extensive enough to permit determination of minimal and optimal dosage. In general the usual dose has been 1000 mgm. or 50 cc. of 2 per cent saccharated iron oxide. Doses have ranged from 600 to 1430 mgm. in individual patients. Maximum single dose was 200 mgm. Details are discussed in the case reports. Standard administration of the iron has followed for the most part the accompanying schedule:

Day 1	1 cc. or 20 mgm.
Day 2	3 cc. or 60 mgm.
Day 3	6 cc. or 120 mgm.
Day 4,5,6,7	10 cc. or 200 mgm.

As experience was gained it was found that the 1 cc. and 3 cc. doses could be given the same day. These smaller doses were used to test for individual sensitivity to the drug. In many instances the patients were treated as out-patients coming daily to the clinic for the iron injection.

Size #22 and #20 needles have been used for administering the saccharated iron oxide. The smaller bore needle is probably better in that too rapid injection is not possible and backflow of the iron solution into surrounding tissue is prevented. A needle of this calibre also reduces the trauma to the vein. It is recommended that injection not exceed 1 cc. per minute. The one generalized type reaction probably resulted from too rapid injection of a relatively large dose.

5. Toxic Reactions

The usual toxic manifestations following intravenous iron injection have been described by Goetsch and Moore[1]. They include nausea, vomiting, nasal stuffiness, sneezing, lacrimation, parasthesias, flushing of face, palpitation, pounding headache and backache. Fever usually followed the injection. Blood pressure drops, sometimes alarming, tachycardia, substernal oppression and diarrhea occur less frequently. Local reaction was chiefly pain and thrombophlebitis.

In the majority of cases to be reported, treatment with saccharated iron oxide produced no toxic symptoms. In only one instance was anything resembling

*It is to be noted that the saccharated iron oxide used in this study was doubly autoclaved. In a letter from Sharp and Dohme it was stated that subsequent lots of saccharated iron oxide will be autoclaved only once in the vial, the bulk material to be sterilized by Seitz filtration.

a generalized reaction seen. This will be described in detail. In no case was thrombophlebitis produced. Temperature elevations were not observed and the vein remained in condition suitable for repeat injection throughout the treatment period. Considerable trauma was produced to the veins because frequent blood samples were being drawn for iron and routine blood determinations. Local reactions were mild. In two cases the saccharated iron oxide was inadvertently injected outside the vein with production of pain in this area. In neither instance was there any fibrosis or slough.

One individual had a generalized type of reaction following the 5th injection. She received 10 cc. for a total dose over 5 days of 600 mgm. About two minutes after completion of the injection, sharp pain was felt in the pit of the stomach. This was followed by flushing of the face, a pounding headache, and nausea. Blood pressure and pulse remained normal. The attack passed off within 3 minutes and the patient resumed her normal activity without further effect. No further injections were given this individual. It is likely that the injection had been too rapid. Using smaller needles and more deliberate injection in subsequent patients, we have observed no similar injection reaction.

6. Results of Therapy

Methods employed for determinations to be reported have been previously described[8]. Fourteen patients have been treated with saccharated iron oxide with complete or nearly complete results. Several additional patients are under therapy at this time. In this group of 14, six patients had a mild to moderate iron deficiency anemia associated with pregnancy. Four normal pregnancy patients were treated. Two of the group were mildly anemic but no iron deficiency was manifest. Bone marrow studies on these permit their classification as refractory anemia associated with hypoplasia of the bone marrow. One post partum hemorrhage and one menorrhagia complete the group. Since the total number of cases is small, each case will be presented individually.

Table 1 shows the results in the first case to be treated with saccharated iron oxide. The diagnosis was moderate iron

Table 1

F.C. Age 28: Para 1-0-0-1; Diagnosis: Iron Deficiency Anemia.
Total dose of saccharated iron oxide was 1430 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
5-18	7.1	3.86	28	1.9	301	600	10	Oral iron
6-14				4.3				Maximum retic. response
7-12	8.6	3.79	32	2.8	106	575	15	
7-18								I.V. iron started
7-27						250	188	Fasting value
							680	5 min.after I.V.iron
							387	24 hr.after I.V.iron
8-2				4.5				Retic. response
8-8	10.3	4.24	37	1.8			154	
9-7	12.8	4.10	44	1.6			88	
9-12	13.1	4.24	42	0.8	56	350	70	
9-20								Cesarean section

deficiency anemia. The bone marrow picture was typical. The low serum iron, high erythrocyte protoporphyrin and high iron binding capacity confirmed the diagnosis. The iron tolerance curve showed a maximum serum iron of 60 gamma % 4 hours after ingestion of the test dose of oral iron.

Clinical trial with ferrous gluconate* gram 1 t.i.d. produced a slight reticulocyte response and only a slow replacement of hemoglobin. Subsequent administration of 1430 mgm. of saccharated iron oxide produced a second reticulocyte response and rapid regeneration of hemoglobin. This patient was delivered by cesarean section at which time a liver biopsy was obtained. Sections stained with appropriate iron stains showed iron in the Kupffer cells lining the liver sinusoids. The liver itself appeared normal. No toxic symptoms were noted on multiple injections of iron.

A marked increase in blood values in a second case is shown in Table 2. The maximum reticulocyte rise to 8.3 per cent is the highest observed in pregnancy iron deficiency anemia in our series. The value of complete filling of the iron stores is illustrated by the continued improvement after delivery. No reaction was noted in this patient.

Table 2

J.W. - Age 19 - Para 0: Diagnosis: Iron Deficiency Anemia.
Total dose of saccharated iron oxide was 1000 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
9-6	9.4	3.23	32	0.6	81	450	30	I.V. iron started
9-15							836	15 min. after I.V. iron
9-17				8.3				Maximum retic.response
9-19	11.3	4.13	37	4.4		390	151	
9-24								Normal delivery
9-27	13.3	4.28	43	2.9	69		400	
10-4	13.8	4.99	45	1.3	59	300	32	
11-1	13.9	5.10	43	1.5	64		40	

In Table 3 the results of therapy following post partum hemorrhage are shown. This is not the recommended therapy for post partum hemorrhage but in selected cases may be of value. A second similar case is under treatment at this time where attempts at transfusion have produced reactions severe enough to discourage further attempts. Regeneration of hemoglobin was probably accelerated by comparison with untreated post hemorrhagic regeneration.

The results shown in Table 4 are of interest. Preliminary treatment with oral iron produced no response. Subsequent therapy with saccharated iron oxide produced a satisfactory response which has continued since delivery. This is the fourth iron deficiency anemia investigated in the last 6 months which has failed to respond to oral iron. It suggests that partial or complete failure of iron absorption in pregnancy may be more frequent than previously suspected. This patient was treated as an out-patient. No reaction was observed.

The cases shown in Tables 5 and 6 were treated just prior to delivery. Most of the improvement in the blood picture followed delivery. Reticulocytes were not followed in Case 5 in that she was treated as an out-patient. In

*Ferrous gluconate gr. V used in this study was supplied by Eli Lilly & Co.

Table 3

P.L. - Age 17 - Para 0: Diagnosis: Post Partum Hemorrhage
Total dose of saccharated iron oxide was 800 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
7-21	14.2							Normal pregnancy
8-8	8.0	2.32	24	1.4	63		38	P.P. hemorrhage Blood loss 800 cc. I.V. iron started
8-15	8.7	2.14	26.5				575	Completed iron therapy
8-16				8.5				Maximum retic. response
8-26	9.5	3.10	29	0.8			66	
9-2	11.4	3.54	36	0.6		185	80	
9-20	13.5	4.04	43	1.4	81	240	24	

Table 4

C.D. - Age 23 - Para 2-0-0-2: Diagnosis: Iron Deficiency Anemia
Total dose of saccharated iron oxide was 800 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
7-1	9.7	2.97	30	1.8	84	380	35	Oral iron
8-17	9.6	2.42	29	1.8			35	
8-22	9.2	3.11	29	1.6	123	445	35	I.V. iron started
9-14	11.8	3.20	35	2.0		330	136	
9-28	11.4	4.05	37	0.8	65	350	80	
10-1								Normal delivery
10-5	12.8	3.82	41	1.1	62	300	79	
11-3	13.3	3.98	43	0.8	53	150	118	

Table 5

E.R. - Age 22 - Para 4-0-1-4 Diagnosis: Iron Deficiency Anemia
Total dose of saccharated iron oxide was 1160 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
8-4	8.6	3.41	27	1.0	66	500	17	I.V. iron started
8-11	8.9	3.12	28	3.0	58	100	617	Iron therapy completed
8-17	9.4	3.73	30	1.6			137	
8-26	10.0	3.43	31	0.4			124	
8-30								Normal delivery
9-6	12.7	3.84	39	1.7	92	300	86	
11-3	14.5	5.01	40	0.6	53		108	

Table 6

M.S. - Age 35 - Para 0-1-1-0: Diagnosis: Minimal Iron Deficiency Anemia. Total dose of saccharated iron oxide was 940 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
7-3	9.4	4.1						
7-18	10.7	4.25	35	1.2	71	425	63	I.V. iron started
7-22							700	5 min. after I.V. iron
							630	3 hr. after I.V. iron
7-28	10.8	3.75	35	3.1		245	190	In labor
7-29								Delivery
8-8	10.2	3.26	34	5.0			68	
8-11	12.3	4.12	40	4.2	42	300	70	
9-15	13.2	4.50	42	0.8	43	200	91	

neither individual was any toxic reaction noted.

Table 7 shows the results in a gynecologic case. Profuse and prolonged menses undoubtedly caused the anemia. This patient had attempted oral iron therapy for two years but was intolerant to all of the various iron salts. In two years, a hemoglobin above 70% was not seen. A curettage has failed to alleviate the profuse menses. She was given 1000 mgm. of saccharated iron oxide as an out-patient. On one occasion a small amount of the material was injected outside the vein. Local tenderness persisted for about an hour. No fibrosis or necrosis has been seen. Response to therapy has been satisfactory but in the face of continued menstrual excess it will be of interest to observe subsequent blood values. In Table 8 is shown the results of therapy in the last iron deficiency anemia of pregnancy. Treat-

Table 7

I.M. - Age 25 - Para 1-0-1-1 - Diagnosis: Menorrhagia
Total dose of saccharated iron oxide was 1000 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
9-12	9.9	4.10	35	1.0	134	370	7	I.V. iron started
9-23							120	Fasting value
							584	5 min. after I.V. iron
9-24				4.9				Maximum retic. response
9-27	10.8	4.37	37	3.1				
10-6	11.8	3.94	39	1.0			70	
11-3	13.5	4.99	44	0.6	92		60	

Table 8

B.M. - Age 15 - Para 0: Diagnosis: Iron Deficiency Anemia
Total dose of saccharated iron oxide was 1000 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
9-6	10.7	3.01	32	1.5	82	450	57	I.V. iron started
9-14							620	Iron value after I.V.
9-16				3.5			418	Maximum retic. response
9-19	11.4	3.78	37	2.8			205	
9-22						300	138	
9-27	11.7	3.84			52	295	125	
10-4	11.7	3.58	37	1.1	52	290	150	
10-11	13.1	4.19	39	1.2		395	135	
10-19								Normal delivery

ment was taken without complication.

In previous discussions before the staff, the concept of bone marrow hypoplasia resulting in a refractory anemia of pregnancy has been advanced.[8,20] It has been of interest to subject two individuals with this syndrome to intensive iron therapy. Normal serum iron and normal erythrocyte protoporphyrin values would indicate that iron therapy should be relatively ineffective. Oral iron therapy has previously been reported as non-effective. In the two cases illustrated briefly in Table 9, only minor responses have followed intravenous iron therapy. This would seem to be additional proof of the concept inasmuch as the blood picture in the normal pregnancy, as will be subsequently shown, responds to intravenous iron therapy.

Four normal pregnant women have been

Table 9

Response of cases with bone marrow hypoplasia treated with saccharated iron oxide. Dose in each case was 1000 mgm.

Date	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
V.W. Age 21 - Para 0 - Diagnosis: Bone marrow hypoplasia								
9-28	9.9	3.57	34	1.2				
10-3	11.0	3.84	35	2.1	64	400	78	I.V. iron started
10-17				3.1				Maximum retic. response
11-3	11.6	4.29	38	1.2	47	200	116	
V.W. Age 28 - Para 0 - Diagnosis: Bone marrow hypoplasia								
10-14	10.5	3.69	32	2.7	53	300	87	I.V. iron started
11-3	11.4	3.83	36	0.4	54	150	76	

given intravenous iron. Each of the four made an excellent response to the iron medication. Similar responses have been observed with oral iron therapy but will not be presented. For comparison the average values for blood values in pregnancy obtained from investigation of 70 pregnant women are shown in Table 10.

Table 10

Normal Pregnancy. Average values of 70 patients examined in various months of pregnancy

Month	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % S.I.	Gamma % I.B.C.	Gamma % E.P.
3	12.6	4.12	38.7	1.4	100	216	48
4	12.2	3.93	37.2	1.2	95	243	43
5	11.9	3.74	37.0	1.3	104	277	47
6	12.4	3.99	38.9	1.7	96	297	42
7	11.9	3.84	37.2	1.2	102	282	44
8	11.9	3.80	36.9	1.0	64	343	48
9	12.1	3.99	37.5	1.2	73	396	58
P.P.	12.0	3.96	38.3	1.1	53	255	71

These were untreated cases. In many instances serial determinations were done monthly throughout pregnancy so the number of determinations is greater than 70. This series represents a selected group in that individuals with low hemoglobins were taken out for more detailed study. A slight decrease in hemoglobin, erythrocyte count and hematocrit values is shown in the third trimester with the tendency toward improvement in the last month. Of interest is the significant decrease in the serum iron and elevation of the iron binding capacity in the last two months of pregnancy. In the presence of normal hemoglobin and hematocrit values the observed changes would indicate a latent iron deficiency. It probably represents the large transfer of iron to the fetus. Similar findings have been reported by Fay, Cartwright and Wintrobe[21]. If the fall in serum iron and rise in iron binding capacity were the result of hemodilution and not the result of a relative iron deficiency, oral or intravenous iron therapy should have no effect on these values. Results of routine intravenous iron administration in four normal pregnancies are shown in Table 11. All the values are not shown but the serum iron values remained high and the iron binding values remained within normal limits in all cases. Hemoglobin values were about 13 gm.% or better at the time of delivery. These findings would indicate that hemodilution is not so much a factor in reduced hemoglobin values in pregnancy as previously thought, but that in nearly every pregnant woman a relative iron deficiency exists which can be corrected by appropriate iron therapy. It was the fourth patient in this group who had the generalized reaction previously described. Only 600 mgm. was administered with results comparable to those individuals who received larger doses. This would suggest that for routine use in pregnancy a dose of 600 mgm. might be optimal therapy. Obviously further observations are necessary.

7. Discussion and Conclusion

As yet only cautious general conclusions can be reached. It is probable that saccharated iron oxide will be found to have a definite place in the

Table 11

Response to saccharated iron oxide in four normal pregnancies. Total dose in each case was 1000 mgm.

	Month	Gm.% Hgb.	Million R.B.C.	% H'crit.	% Retic.	Gamma % E.P.	Gamma % I.B.C.	Gamma % S.I.	Remarks
I	7	11.3	3.35	36	1.4	27	225	120	I.V. iron started
	9	13.3	4.39	41	1.9	43	200	170	
	P.P.	13.1	3.94	40	2.4	57	145	106	
II	6	12.0	3.68	37	0.8	24	335	60	I.V. iron started
	9	13.7	4.40	42	1.5	27	225	98	
	P.P.	15.6	4.40	48	0.8	23	245	145	
III	7	10.7	3.46	35	1.2	38	335	25	I.V. iron started
	9	12.7	4.1	41	1.6	50	215	65	
IV	7	11.1	3.40	35	0.6	55	400	50	I.V. iron started **
	9	13.9	4.50	41	1.4	49	285	80	
	P.P.	13.7	4.03	41	2.0	46	390	55	

** This individual received only 600 mgm. because of reaction.

treatment of iron deficiency states. It is not without toxic effects but by comparison with other iron preparations it is a reasonably safe material for intravenous injection. More detailed chronic toxicity studies are needed.

It is possible that encephalitis could be produced by an intravenous iron injection. There is always the possibility of liver injury with resulting cirrhosis. An exogenous type of hemochromatosis similar to that observed following multiple blood transfusions might result from repeated injections of iron. Long period observations on individuals who have received intravenous iron are necessary.

The effectiveness of saccharated iron oxide where iron deficiency exists can hardly be questioned. With demonstration that a large percentage of the injected iron is utilized for hemoglobin synthesis one should expect maximum response from its use. Our own brief experience with that of other investigators would suggest this to be true.

The indications for its use have only partially been explored. Pregnancy anemias produced by iron deficiency in several of our series have failed to respond to oral iron therapy. Govan and Scott[17] report 3 similar cases in pregnancy. In these the intravenous administration of iron offers the only cure short of blood transfusion. In pregnancy the time factor is likewise of importance. Most iron deficiency anemias of pregnancy are manifest in the last trimester. Oral iron therapy may be effective but absorption of iron at best is slow. The intravenous administration of iron permits the maximum bone marrow response. Intolerance to iron salts given orally is frequently seen. This is especially true in pregnancy. This is the third indication for its use in Obstetrics.

Under investigation now is a case of iron deficiency anemia associated with carcinoma of the cervix. Oral iron is contraindicated where massive doses of x-ray are being given. In the past transfusions have been used freely. These are troublesome and expensive. It seems likely that the use of intravenous iron would be useful in surgical patients where resection or disturbance of the gastrointestinal tract does not permit adequate iron absorption. Other indi-

cations for the use of intravenous iron certainly exist.

Little mention has been made of the clinical response aside from the blood picture. It is hard to evaluate because a certain psychological factor is added by the special attention afforded this group of patients. As a general impression the tired and weak feeling so often found in association with anemia disappears rapidly. Many of the individuals reported marked improvement in their own sense of well-being after completion of therapy.

8. Summary

(1) Saccharated iron oxide has been administered in 12 patients with various clinical iron deficiency states. It has produced a satisfactory response in these patients without serious toxic reaction. In three cases it was effective where oral iron had failed either because the oral iron was not tolerated or was not absorbed.

(2) In the pregnancy anemia associated with hypoplastic bone marrow, saccharated iron oxide is not effective.

(3) The general indications for the use of saccharated iron oxide have been advanced:

a. Where oral iron is not effective or not tolerated

b. Where rapid regeneration of hemoglobin is desirable

c. Where there has been extensive depletion of iron stores.

(4) The properties of saccharated iron oxide have been discussed. The dose and method of administration have been presented. By comparison with other iron preparations, saccharated iron oxide is relatively non-toxic. Further clinical investigation is indicated.

References

1. Goetsch, A. T., Moore, C. V., and Minnich, V.
Observations on the effect of massive doses of iron given intravenously to patients with hypochromic anemia.
Blood 1: 129, '46.

2. Stockman, R.
Treatment of chlorosis by iron and some other drugs.
Brit.Med.Jr. 1:881 and 942, 1893.

3. Heath, C. W., Strauss, M. B., and Castle, W. B.
Quantitative aspects of iron deficiency in hypochromic anemia.
Jr.Clin.Invest.11:1293, '32.

4. Whipple, G. H. and Robscheit-Robbins, F.S.
Iron and its utilization in experimental anemia.
Am.Jr.of Med.Sci.191:11, '36.

5. Hahn, P. F., and Whipple, G. H.
Iron Metabolism: its absorption, storage and utilization in experimental anemia.
Am.Jr.of Med.Sci. 191:24, '36.

6. Witts, L. J.
Discussion on the treatment of anemias.
Proc.Royal Soc. of Med. 26:607, '33.

7. Finch, C. A., Gibson, J. G., Peacock, W. C. and Fluharty, R. G.
Utilization of intravenous radioactive iron.
Blood, 4:905, '49.

8. Holly, R. G.
Iron metabolism in pregnancy.
Bull. of U. of Minn. Hosps. 20:475, '49.

9. Cappell, D. F.
Results of intravenous injection of colloidal iron.
Jr. of Path. & Bact. 32:595, '29.

10. Cappell, D. F.
The late results of intravenous injection of colloidal iron.
Jr. of Path. & Bact. 33:175, '30.

11. Polson, C. J.
Fate of colloidal iron administered intravenously.
Jr. of Path. & Bact. 31:445, '28.

12. Polson, C. J.
The storage of iron following its oral and subcutaneous administration.
Quarterly Jr. of Med. 23:77, '29.

13. Mannich, C. and Rojahn, C. A.
(Cited by Slack and Wilkinson)
Ber. dtsch. pharm. Ges. 32:158, '22.

14. Nissim, J. A.
Intravenous administration of iron.
The Lancet 253:49, '47.

15. Davidson, L. S. P. and Girdwood, R.H.
Refractory iron deficiency anemia treated with intravenous saccharated oxide of iron.
Brit.Med.Jr. 1:733, '48.

16. Slack, H. G. B. and Wilkinson, J. F.
Intravenous treatment of anemia with an iron-sucrose preparation.
The Lancet 256:11, '49.

17. Govan, A. D. T. and Scott, J. M.
Intravenous iron in the treatment of anemia of pregnancy.
The Lancet 256:14, '49.

18. French, D. G.
Intravenous treatment of anemia with an iron-sucrose preparation (Letters to Editor)
The Lancet: 256:370, '49.

19. Ross, C. A., McKinney, S. E., Peck, H. M. and Beyer, K. H.
A pre-clinical evaluation of saccharated iron oxide.
Personal communication, to be published.

20. Holly, R. G.
Anemias of pregnancy.
Bull.of U. of Minn. Hosps.:17:281,'46.

21. Fay, J., Cartwright, G. E. and Wintrobe, M. M.:
Studies on free erythrocyte protoporphyrin, serum iron, serum iron-binding capacity and plasma copper during normal pregnancy.
Jr. of Clin.Invest.28:487, '49.

II. MEDICAL SCHOOL NEWS

Coming Events

November 28-December 3 - Continuation Course in Child Psychiatry for General Physicians and Pediatricians.

December 9 - Annual meeting of the Minnesota Medical Foundation, Campus Club, Coffman Memorial Union, 6:30 p.m.

December 16-17 - Continuation Course in Obstetrics for General Physicians.

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Alumni News

Dr. Byarne Houkom, who left his Minneapolis practice in Ophthalmology, is now active in medical work in the mission field in Tanganyika Territory, East Africa.

Dr. E. S. Mariette has recently resigned his position as Director of the Glen Lake Sanitorium because of his health. Friends of Dr. Mariette may reach him by writing him at RFD #3, Wayzata, Minnesota.

Dr. Harold L. Neuenschwander has recently become associated with the Department of Allergy and Internal Medicine of the Acuff Clinic, Knoxville, Tennessee.

Dr. Henry E. Michelson, Chief of the Division of Dermatology has informed us of the addresses of the following physicians who formerly received graduate training at the University of Minnesota in Dermatology.

Dr. George D. McAfee is associated in the practice of dermatology with Dr. A. L. Welsh in Cincinnati, Ohio.

Dr. Warren McCauley is a member of the Fargo Clinic, Fargo, North Dakota.

Dr. John Schmidt and Dr. John Barthel are active in the private practice of dermatology in Duluth, Minnesota and Lincoln, Nebraska, respectively.

Faculty News

Dr. Wesley W. Spink was elected President of the Central Society for Clinical Research at its recent meeting in Chicago. Dr. Spink had previously served as a member of the council.

Dr. Leo Rigler, Head of the Department of Radiology, will present a teaching course in "Acute Abdominal Conditions" at the meeting of the Radiological Society of North America in San Francisco in December. He will also be chairman of the symposium on Cardiac Roentgenology for the Society. While he is on the West Coast, he will participate as one of the speakers in the Gastric Cancer Conference in San Francisco on December 13 and will present the subject "Newer Trends in Cancer Diagnosis".

Child Psychiatry

A continuation course in Child Psychiatry will be presented at the Center for Continuation Study on November 28 through December 3. The course, which is presented for pediatricians and general physicians, will concern itself first with normal emotional, intellectual, and social development. Later in the course there will be presented a discussion of various types of emotional problems, sources of anxiety, and the relation of emotional problems to physical growth.

Dr. Adrian Vander Veer, of the Department of Psychiatry, University of Chicago, and Dr. Griffish Binning, of Saskatoon, Saskatchewan, will participate as visiting faculty members for the course. Dr. Reynold Jensen, Associate Professor of the Department of Pediatrics, University Hospitals, is directing the course and will be joined by clinical and full-time members of the faculty of the Medical School and Mayo Foundation.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

November 20 - November 26, 1949

No. 265

Sunday, November 20

9:00 - 10:00 Surgery Grand Rounds; Station 22, U. H.

10:30 - 11:00 Surgical Conference; Anemia after Lateral Intestinal Anastomosia; Robert Toon; Rm. M-109, U. H.

Monday, November 21

8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Seminar; Ultraviolet Erythema and Pigmentation; C. Robert Dean; E-101, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 1:00 Physiology Seminar; Adaptation to Caloric Restriction; Henry L. Taylor; 214 M. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:20 Pathology Seminar; H. L. Ahrlin; 104 I. A.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Classroom, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Public Health Seminar; Subject to be announced; 113 Medical Science.

4:00 - Pediatric Seminar; Unipolar Lead Electrocardiograph; L. G. Veasy; 6th Fl. W., Child Psychiatry, U. H.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

Monday, November 21 (Cont.)

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy, O. J. Baggenstoss and Staffs; M-109, U. H.

Tuesday, November 22

8:15 - 9:00 Roentgenology-Surgical-Pathological Conference; Craig Freeman and L. G. Rigler; M-109, U. H.

8:30 - 10:20 Surgery Conference; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell; Veterans Hospital.

12:30 - Pediatric-Surgery Rounds; Sta. I, Minneapolis General Hospital; Drs. Stoesser, Wyatt, Chisholm, McNelson and Dennis.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

1:00 - 2:30 X-ray Surgery Conference; Auditorium, Ancker Hospital.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:00 - 5:00 PhysiologypSurgery Conference; Common Channel Phenomenon and Pancreatitis; Carter Howell and Lyle Hay; Eustis Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by General Hospital Staff; Drs. Lipschultz and MacDonald; Todd Amphitheater, U. H.

Wednesday, November 23

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans, Room 1AW, Veterans Hospital.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker; Veterans Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson, and Staffs; Todd Amphitheater, U. H.

Wednesday, November 23 (Cont.)

12:00 - 1:00 Radio-Isotope Seminar; Dosage Determination in Isotope Problems; J. F. Marvin; 113 Medical Science Bldg.

3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.

4:00 - 5:00 Infectious Disease Rounds; General Hospital, Basement Amphitheater.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; E-101, U. H.

Thursday, November 24 -- H O L I D A Y

Friday, November 25

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:45 - 12:50 University of Minnesota Hospitals General Staff Meeting; Football Pictures; Administration; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater, U. H.

4:00 - 5:00 Electrocardiographic Conference; George N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

5:00 - 6:00 Otolaryngology Seminar; Review of Current Literature; Dr. Koller; Todd Memorial Room, U. H.

Saturday, November 26

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; M-109, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Small Classroom, Minneapolis General Hospital.

8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 11:30 Surgery-Roentgenology Conference; Todd Amphitheater, U. H.

9:00 - 11:30 Neurology Conference; Atrophies and Dystrophies; University Hospitals.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 12:00 Anatomy Seminar; The Association Between the Visual Cortex and the Oculomotor Nucleus; Harold Haft; The Effect of Glucose on the Islets of Langerhans; Lewie O. Ingersoll; 226 I. A.