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Treatment of iron deficiency anemias

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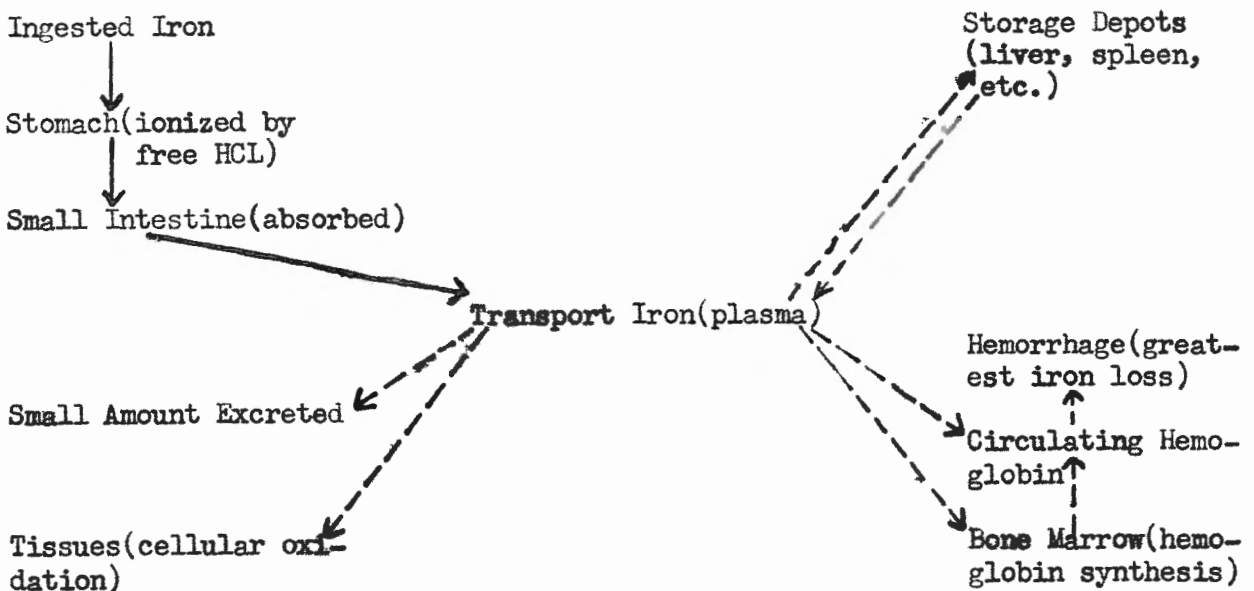
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Purpose of Paper

The purpose of this paper is to consider the effects of various iron preparations, particularly molybdenized ferrous sulfate(M-I)complex, on iron deficiency anemias.

Iron Metabolism

A brief resume of iron metabolism includes the following pertinent facts (11). Iron is absorbed from the gastro-intestinal tract, most of it from the upper portion of the small intestine. Storage depots for iron are the nuclei of cells, the bone marrow, spleen, and liver. Barer and Fowler(9), in studies of the iron requirements needed in the daily diet, found that from 4-7mgm daily produces a negative iron balance, while 12-15mgm of iron daily produces a positive balance. Achlorhydria and hypochlorhydria materially retard the retention of dietary iron and therefore such individuals require a larger daily intake.

Excessive quantities of iron are excreted through the colon and kidney. The absorption of iron is determined by the iron content of the tissues. For example, anemic dogs absorb much more of the metal than normal animals.

A schematic outline(11) of iron metabolism is as follows:

Ingested Iron → Stomach(ionized by free HCL) → Small Intestine(absorbed) → Transport Iron(plasma)

Transport Iron(plasma) → Small Amount Excreted

Transport Iron(plasma) → Tissues(cellular oxidation)

Transport Iron(plasma) → Storage Depots (liver, spleen, etc.)

Transport Iron(plasma) → Circulating Hemoglobin

Transport Iron(plasma) → Bone Marrow(hemoglobin synthesis)

Hemorrhage(greatest iron loss)

Circulating Hemoglobin

Bone Marrow(hemoglobin synthesis)

Iron Deficiency Anemias

Definition-Etiology

Insufficient iron for hemoglobin synthesis will lead to anemia of the hypochromic type, characterized by microcytosis and hypochromia of the individual cells and by a lowered hematocrit. This is referred to as iron deficiency anemia. The most common form results from chronic hemorrhage. It occurs whenever the prolonged loss of iron, in the form of hemoglobin, is more rapid than its replenishment and is encountered most frequently in cases of peptic ulcer, hemorrhoids and menorrhagia.

The cause of idiopathic hypochromic anemia(10) is fundamentally the same. In this syndrome the blood loss is frequently unrecognized menorrhagia, so that no history of excessive bleeding is obtained. Since achlorhydria or hypochlorhydria is usually present, thus resulting in interference with the proper absorption of iron, a blood loss which would be ordinarily of little significance assumes increased importance. In some instances even the normal menstrual blood loss seems to be sufficient to produce an iron deficiency when there is a disturbed gastric secretion.

The types of anemia during pregnancy(8) include:

1. physiologic
2. subnormal hemoglobin plus physiologic
3. macrocytic-pernicious anemia type

Minimum normal values(11) for hemoglobin, erythrocytes and hematocrit in the pregnant woman are, because of the hydremic phenomenon of pregnancy, substantially lower than those in the non-pregnant women. However, Litzenberg questions the amount of emphasis which should be placed on the term "physiologic".

Number two is the microcytic type of anemia(8) and forms the vast por-
tion of anemias of pregnancy, of which, as a rule, the patients have no signs
and symptoms of the condition. This(12) may be due to nourishment demands
of the fetus or diet deficiencies of the mother, particularly iron.

Fowler and Barer(9) state that the anemia associated with pregnancy is
due to the depletion of maternal iron supplies because of fetal requirements,
and the achlorhydria prevents their replacement. On the other hand, Dieck-
mann, Adair, et.al.(7), suggest that the anemia of pregnancy is not due to
the parasitic action of the fetus on maternal iron supplies since the fall
in hemoglobin of the mother is greatest during the first twenty eight weeks
of pregnancy, when fetal requirements are negligible. In the last twelve
weeks of pregnancy, when the fetal weight increases markedly and it would
be supposed that fetal iron requirements would be maximal, maternal hemo-
globin concentration seems to be stationary. Coons and his coworkers have
shown that iron retention is deficient in pregnancy in their series of meta-
bolic studies. Thus the low retentions are not due to low total iron intake
but probably to a deficiency of other dietary factors promoting the utili-
zation of iron. Dieckmann quotes Coons in his article(8) and agrees with
his findings. Neary(5) briefly states that pregnancy is known to impair
body response to iron, perhaps because one or more factors responsible for
the anemia of pregnancy continue to be operative during the period of ges-
tation.

Definitive conclusions may not be made but it is quite possible that
impaired utilization occurs in regard to iron because of disturbed maternal
metabolism.

A diet(10) deficient in iron may lead to a hypochromic, iron deficiency type of anemia. This, of course, becomes especially important when the patient has achlorhydria. Restricted diet and excessive administration of alkalis to patients with peptic ulcers interfere with the replenishment of their iron stores.

Thus, with these types of iron deficiency anemias, iron therapy is needed and effective.

Iron Preparations

Although iron(usually in the form of ferrous sulfate)(4) is regarded as the specific treatment for hypochromic anemias, relatively small amounts of the element are absorbed, and still smaller amounts are utilized, following administration of therapeutically adequate dosages of iron preparations.

Various means of potentiating the therapeutic action of iron, by facilitating absorption or utilization of the metal, have been studied. Thus the use of calcium, cobalt, preformed pyrol substances such as chlorophyll and "secondary anemia" liver extract have been made in attempting to increase absorption and/or utilization of iron. The value of such "accessory substances" is doubtful.

The majority of experimental work(5) for investigating possible catalysis of iron by "accessory substances" has been directed towards copper. Although copper does have a place in hemopoiesis, it functions to allow better utilization of iron only in animals made anemic by a diet deficient in both copper and iron, as in an exclusively milk diet. Thus its role is necessarily restricted to a very few individuals, mainly young infants, with hypochromic nutritional anemias. In adult hypochromic anemia(9) the addition

of copper to suboptimal doses of 100mgm/day of ferric iron fail to produce an optimal response.

That the additions(9) of vitamins of the B complex, liver and stomach extracts do not appear to enhance the action of iron, <u>even in a low income group</u>, has been emphasized. Folic acid(1) does not seem to be of value either in potentiating the action of iron.

The most recent addition to the "accessory substance" list is molybdenum. The hemopoietic agent is a molybdenum-iron(M-I) complex(4) in which molybdenum sesquioxide(Mo_2O_3) and ferrous sulfate are co-precipitated to produce a homogeneous mass containing a partial physical union of the component salts. Its effectiveness as a therapeutic agent will be considered in certain of the following paragraphs.

Response to Therapy

The therapeutically induced recovery period according to Barer and Fowler(9) in iron deficiency anemias is divisible into three phases:

1. a rapid regeneration phase lasting about two months

2. a "therapeutic overshoot" occurring in the third month

3. a return to the patient's normal level between the fourth and sixth month. They also feel that iron therapy must be given for at least three months for maximal response and adequate replacement of depleted stores. The dosage of 250mgm of elemental iron(equivalent of 25grs of ferrous and ammonium citrate, 10grs of ferrous sulfate, or 33grs of ferrous pyrophosphate) appears to be adequate. They note no difference in response between ferrous and ferric salts of iron.

Response to Therapy(con't)

A. Uncomplicated Hypochromic Anemia

In the following paragraphs the therapeutic value of molybdenum-iron complex, as compared to iron alone(ferrous sulfate), in the treatment of iron deficiency anemias will be considered as well as the time differences, when using M-I complex, as compared to the schedule noted above.

Healy(4) treated a series of patients who had moderately severe hypochromic anemia, either on the basis of protracted hemorrhage or associated with a state of gross malnutrition. The results are as follows:

	Initial Hgb.	Rate of Hgb. Regeneration	Dosage(Elemental Iron)
GroupI (Treated with M-I complex)	8.41gms%	0.36gms%	230mgm
GroupII (Treated with FeSO₄)	8.18gms%	0.12gms%	380mgm

The patients in Group I attained normal hemoglobin levels within a period of time varying from nine to thirty one days and averaging thirteen and seven tenths days. In Group II in a period ranging from fifteen to twenty four and averaging twenty and seven tenths days, during which time the results of treatment were observed, only two patients attained a hemoglobin level as high as 12gms%. Normal hemoglobin values were not reached in the other patients during the period of observation. Other pertinant findings noted include the tripling of the daily average rate of hemoglobin regeneration in patients treated with M-I complex and the almost uniform rate of hemoglobin formation throughout treatment. There was no progressive slowing of hemoglobin formation and definite retardation occurred only after normal values had actually been reached.

Kelly(3) was able to study only two patients satisfactorily. In these the anemia was rather severe(5.7-6.0gms%). Treatment consisted of five weeks therapy with M-I complex, supplying 160mgm of elemental iron daily. Weekly hemoglobin gains of 1.1 and 1.6gms% were noted which suggested to the author that the preparation is a potent therapeutic agent in iron deficiency anemias.

B. Hypochromic Anemia of Pregnancy

The subject of anemias of pregnancy is complex and rather abstruse, concerning both etiology and treatment.

According to Dieckmann, et.al.(8), the blood findings during pregnancy are: Hgb.-11.56gms%, cell volume-37.31vol%, RBC-3.77million. Minimum standards are: 10gms%, 33vol%, and 3.36 million. These standards have been used by most investigators in this field. In his survey in 1936(8) Dieckmann showed that 11.6% of his patients were anemic or 63.2% if normal standards were used. In 1947(2) there were only 4.6% with anemia of pregnancy or 39% according to nonpregnant standards.

Dieckmann and associates have studied anemias of pregnancy and their treatment for several years. A composite of their results reveals:

1. In 1936(8) the observation was made that hemoglobin increases were quite similar in the treated and the control groups. There was little difference in hemoglobin rises in those treated with ferrous and ferric salts and in those who received no iron therapy.

2. In 1944(7) a group of patients were followed through pregnancy and the puerperium to determine if the additions of calcium, potassium, iron or vitamins A or D to the diet had any effect on the course of pregnancy, prevented complications from developing, or insured a higher incidence of normal infants.

No effects were noted. Even those groups that were given iron failed to show any marked variation in hemoglobin concentration.

3. In 1948(13) The following summary was given, "Two hundred fifty cases of anemia in pregnancy were studied to evaluate the effects of treatment with iron alone and in combination with "accessory substances"(i.e. various vitamin concentrates, desiccated hog stomach and liver extract). Controlled observations indicate that the administration of these substances does not increase the rate of hemoglobin formation significantly."

4. However in 1949(2) Dieckmann and associates, using the same method as in all previous studies arrived at the following conclusions on forty nine patients(of which 81% had a microcytic type anemia) treated with M-I complex. Forty five patients gained an average of 2.11gms% hemoglobin before delivery. Their most outstanding finding was that nearly all of the patients showed no further decrease in hemoglobin concentration. They state that they have never used iron salts as effective as M-I complex in pregnant patients. "Our results were so striking that, if the patient has taken this medication for three weeks and shown no significant increase in the hemoglobin concentration, the therapy is stopped and more extensive studies(bone marrow biopsy, gastric analysis, reticulocyte count) are made to determine the cause of the anemia." Because of the hemoglobin increase the possibility of the loss of the "hydremia of pregnancy" was considered, but blood studies revealed no decrease in plasma volume.

Patients so treated had a mean hemoglobin at term of 11.8gms% which is considered high for pregnant patients. And when these women were checked six weeks post partum the hemoglobin readings averaged 12.2gms%, compared with 11.2gms% for the control group. As the minimum in nonpregnant women is

12.0gms% many of the patients were still anemic six weeks post partum.

Continuing with another investigator's findings in iron deficiency a-
nemia of pregnancy, one finds that Neary(5) concludes that the subnormal
levels of hemoglobin readings in pregnant women results from suboptimal dos-
ages. Using normally effective doses(for uncomplicated hypochromic anemia)
over a period of 6.9 weeks, a control group showed an average gain of 2.1gms
% hemoglobin(from 9.1 to 11.2gms%) at the completion of the test period.
However there was renewed therapeutic response when a 50% increase in the
daily amount of ferrous sulfate was taken. But Neary does state that even
this response was less than that noted in the group treated with M-I complex,
showed an average hemoglobin gain of 4.6gms%. Again, increases in hemoglob-
in appeared to follow a distinctive pattern for there was uniform rapidity
in rise until normal levels were almost attained.

Thus their findings showed that a daily dosage of 240mgm of ferrous iron
was suboptimal, when in the form of ferrous sulfate, but therapeutically sat-
isfactory when given as molybdenized ferrous sulfate. Neary also notes that
while use of ferrous sulfate results in an initially satisfactory response
there is a gradual leveling off of hemoglobin levels, "plateau-like", while
patients still have subnormal hemoglobin readings. Substitution of M-I com-
plex resulted in increases in hemoglobin concentration in every patient tested.

Gastro-intestinal Tolerance to Iron Preparations

In all studies of therapy in iron deficiency anemias the question of
gastric tolerance arises. This is especially important during pregnancy and
in organic digestive disorders. Another consideration is the fact that iron
therapy is most easily and effectively given by the oral route.

Findings of several investigators are as follows. Neary(5) noted no gastro-intestinal intolerance in any of the eleven pregnant patients whom he treated with M-I complex. Healy(4) treated forty nine patients suffering from uncomplicated hypochromic anemia with M-I complex, of which only one complained of mild distress, abdominal cramps, which disappeared when the dosage was lowered. Almost one third(six patients) of the twenty one patients on ferrous sulfate therapy alone complained of gastro-intestinal disturbances, of which one was forced to stop medication, while the others were alleviated by lowering the dosage. The most extensive work in the field has been done by Kelly(3) who states, "It hass been estimated that approximately 25% of patients, to whom therapeutically adequate doses of iron salts are administered, develop some degree of gastro-enteric disturbance." This is frequently avoided by building up a "tolerance" in these individuals by giving initially small doses and gradually increasing them to therapeutic levels or at least to gastro-intestinal intolerance levels. This may occassionally be impossible particularly in patients with gastro-intestinal disturbances. In Kelly's series his nineteen patients were regarded as "iron intolerant" on the basis of previous iron salt therapy because of marked gastro-intestinal disturbances resulting from treatment. Fourteen of the patients had organic or functional digestive disease. The other five had infectious or metabolic disease. All of the patients had hypochromic anemia(mild to severe). Treatment consisted of 160mgm of elemental iron daily in the form of M-I complex. In only two patients were gastro-intestinal symptoms so pronounced that treatment had to be discontinued. In other words the percentage of intolerance decreased from 100 to 10%.

M-I Complex

The mode of action of M-I complex is obscure. In four normal adults
(5) there was no significant difference in degree of iron absorption. This
suggested that molybdenum causes in vivo catalysis of iron or stimulates
erythropoiesis, or, stated in different words(4), an example of potentiation
of a therapeutic agent(iron). The reason for greater gastro-intestinal tol-
erance to M-I complex, as theorized by Kelly(3), is that the combination of
molybdenum and iron prevents "oxidation of the ferrous ion into the more a-
strigent trivalent state" in the gastro-intestinal tract. Another factor,
as explained by Kelly, is the more basic reaction(pH6.1) of M-I complex as
compared to ferrous sulfate(pH 4.7), for it is thought that "the degree of
acidity of a dissociated iron salt" may account, at least in part, for di-
gestive reactions noted in ferrotherapy.

Conclusions

The conclusions of several investigators in the field of iron deficiency
anemias point to the use of ferrous sulfate, without "accessory substances",
as a specific in therapy, but that superior therapeutic effects result from
the use of molybdenized ferrous sulfate in the following ways:

1. more rapid response to therapy

2. increased response to therapy-as in anemia of pregnancy

3. greater gastro-intestinal tolerance.

References

1. Chesley, R.F. and Annitto, J.E.: Evaluation of Molybdenized Ferrous Sulfate in the Treatment of Hypochromic Anemia of Pregnancy, Bull. Margaret Hague Mat. Hosp. 1:68 (September) 1948.

2. Dieckmann, W.J. and Priddle, H.D.: Anemia of Pregnancy Treated with Molybdenum-Iron Complex, Am.J. Obstet. and Gynec. 57:541 (March) 1949.

3. Kelly, H.T.: Gastro-Intestinal Intolerance to Orally Administered Iron, Penn. Med. Jl. 51:999 (June) 1948.

4. Healy, J.C.: Hypochromic Anemia: Treatment with Molybdenum-Iron Complex, J. Lancet 66:218 (July) 1946.

5. Neary, E.R.; The Use of Molybdenized Ferrous Sulfate in the Treatment of True Iron Deficiency Anemia of Pregnancy, Am. Jl. Med. Sc. 212:76 (July) 1946.

6. Talso, P.J.: Anemia in Pregnancy, Jour. Insurance Med., 4:31 (Bec.-Jan.-Febr.) 1948-1949.

7. Dieckmann, W.J., Adair, F.L., Michel, H., Cramer, S., Dunkle, F., Arrhur, B., Costin, M., Campbell, A., Wensley, A.C., Lorang, E.: Calcium, Phosphorus, Iron and Nitrogen Balances in Pregnant Women, Am. Jl. Obstet. and Gynec. 47:357 (March) 1944.

8. Adair, F.L., Dieckmann, W.J. and Grant, K.: Anemia in Pregnancy, Am. Jl. Obstet and Gynec. 32:560 (October) 1936.

9. Fowler, W.M., and Barer, Adelaide P.; The Treatment of Iron Deficiency Anemias, J.A.M.A. 112:110 (No. 2) 1939.

10. Schwartz, S.O. and Armstrong, B.E.: Treatment of Iron Deficiency (Hypochromic Anemia), Miss. Valley M.J. 70: 2-13 (January) 1948.

11. Krantz, J.C., Jr., and Carr, C.J.: The Pharmacologic Principles of Medical Practice, Williams and Wilkins, Baltimore, 1949. Chapter XLVII.

12. Litzenberg, J.C.: Synopsis of Obstetrics, C.V.Mosby, St. Louis, 1947. Chapter XIX.

13. Talso, P.J. and Dieckmann, W.J.: Anemias of Pregnancy, Am. Jl. Obstet. and Gynec. 55:518 (March) 1948.