1967

Treatment of hemochromatosis by rapid venesection : a report of a case

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THE TREATMENT OF HEMOCHROMOTOSIS BY RAPID VENESECTION
A REPORT OF A CASE

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Submitted in Partial Fulfillment for the Degree of

Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1967

Omaha, Nebraska

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Perry G. Rigby, M. D., Department of Internal Medicine, Head of Section on Hematology, Eppley Institute, for his assistance and guidance in preparation of this paper.

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INTRODUCTION

Hemochromotosis was first described by Trousseau[1] in 1865, and since that time has continued to be an entity of constant investigation. The classical triad of pigmented skin, diabetes mellitus and hepatic disease was first described by Hanof and Chauffard[2] in 1882. Von Recklinghausen gave the disease its name in 1889. Sheldon[3] in 1927 postulated that hemochromotosis may be a genetic disease due to an inborn error of metabolism, and in 1935 Sheldon[4] in a classical study, summarized the clinical and pathological features of the disease.

McCance and Widdowsen[5] in 1937 noted that excretion of iron was negligible and neither ingestion of massive doses of iron or many transfusions increased the excretion of iron in urine, but excess iron was stored in the reticulo-endothelial system and parenchymal cells. Hahn[6] in 1943 showed there was an increase in absorption of Fe^{59} in iron deficient humans and postulated that a "mucosal block" prevented excessive absorption of iron in normal subjects. Conrad and Crosby[6] in 1963 demonstrated the absorption of Fe^{59} into newly formed epithelial cells of the duodenal-jejunal junction; the migration of these cells from the crypts to the area of sloughing at the tips of the villi and the effect of the iron depletion and iron repletion upon absortion of Fe^{59} into the mucosal cell. Crosby[8] in 1963 proposed that any idiopathic increase in storage iron may represent an inborn error in metabolism with inability of the cell to form ferritin. He theorized that the

intrinsic iron incorporated with apoferritin to form ferritin in the young epithelial cell is not present as a stage of absorption but is permanently retained in the cell to prevent further absorption of iron.

MacDonald[9] in 1963 proposed that hemochromotosis is acquired and previous theories, i.e. "mucosal block", genetic, etc. are not necessarily valid. He stated that hemochromotosis is acquired, and therefore preventable. It is a variant of portal cirrhosis and is really a result of two co-existing situations; one causing cirrhosis, and the other, excessive tissue iron. The fact remains, however, that hemochromotosis exists and is seen in approximately 1:449 autopsies and 1:20,000 hospital admissions[10], admittedly rare, but one that must be diagnosed and treated.

FERROKINETICS

The currently accepted concept of normal iron metabolism is thus. Total body iron is approximately 4.5 gm., the majority of which is contained in the circulating erythrocyte (2.5 gms.). Approximately 600mgm. is present in the labile pool and marrow red cells[11]. Muscle myoglobin contains 140 mgm., and very small amounts are present in the plasma iron pool and in the various iron containing enzymes. The remainder, (approximately 1 to 1.5 gms.), is stored in the tissues in the form of ferritin or hemosiderin, the major site of storage being the liver. Loss of iron under normal conditions has been estimated to be 0.5 to 1.5 mgm. daily in the adult male. Once iron has crossed the intestinal barrier it remains within the body except a very small amount, usually

less than 1 mgm. daily which is lost in urine, feces and desquamated skin[32].

IRON ABSORPTION AND TRANSPORT

The average daily diet contains 10 to 15 mgm. of iron and of this amount, between 5 and 10 per cent is absorbed. The per cent of absorption in growing children and menstruating women is slightly higher. Many methods have been used to determine this figure; the most physiologic one is the method of Moore[12] in which the labeling of foods by Fe^{59} is used. From these experiments much has been learned of the factors that affect iron absorption[13]. Smith and Pannaciulli[14] showed that as the dose of iron was raised, the total amount increased steadily, although the percentage absorption decreased when doses over 100 mgm. were given, no further increase in amount absorbed occurred. The presence of phosphates and phytates which form insoluble iron salts tend to depress salt absorption, while addition of ascorbic acid increases absorption of food iron as well as inorganic iron salts[12].

Iron is believed to be absorbed from the duodenum, but patients with partial gastrectomy and duodenal bypass can absorb inorganic iron salts, but show a defect in food iron absorption. Moore[12] found that hydrochloric acid did not increase absorption of iron in subjects with achlorhydria, and Biggs[15] found this to be true of normal gastric juice when tested with iron in the form of labelled hemoglobin. The exact mechanism of transport of iron across the intestinal mucosa is still a subject of investigation. Granick[16] found that iron feeding led to increased synthesis of

apoferritin in the mucosal cell, which is capable of combining with ferric iron to form ferritin, and that accumulation of ferritin in the cell inhibited further absorption of iron. However, Wohler[17] demonstrated that the presence of large amounts of ferritin in mucosal cells does not inhibit iron absorption in animals. It has been shown that iron deficiency causes increased iron absorption and a single phlebotomy will cause increased iron absorption 7-10 days after the bleeding[18]. This suggests that erythropoesis, rather than iron loss is the stimulus for increased absorption[19].

After absorption, ferric iron circulates in plasma bound to the specific iron-carrying protein, transferrin. The level of transferrin in serum is usually measured in terms of iron binding capacity and is usually 250-400 mcg./100 ml. The serum iron level is usually around 100 mcg./100 ml., therefore the SIBC is usually about 30 % saturated. The regulation of SIBC, like iron absorption, is poorly understood. High levels are found in pregnancy and all types of uncomplicated iron-deficiency anemia. Low levels are found in infection and conditions involving impaired protein synthesis, and conditions in which body iron stores are increased.

FERROKINETICS IN HEMOCHROMOTOSIS

In hemochromotosis the SIBC tends to be fully saturated at a level between 200-250 mcg./100 ml. The mechanism of iron turnover has been extensively studied. Injected Fe^{59} is rapidly removed from plasma in the first four to eight hours, then more slowly and constantly in the next 48 hours. Polygrove and Mortimer[11] calculated that 37 mgm. of iron leaves the plasma daily for the marrow,

of which 23 mgm. are utilized for hemoglobin synthesis by red cell precursors, while 14 mgm. returns to the plasma. Approximately 1 mgm. is exchanged daily between plasma and iron stores. Surface counting reveals that the major site of radioiron deposition is the marrow and that radioiron entering marrow is incorporated into maturing erythrocytes. After 24 hours they begin to appear in peripheral blood. The radioactivity of circulating cells rises rapidly, and by the tenth day after injection, 80-90% of the dose can be found in the peripheral red cell mass.

A number of factors may affect the typical pattern of radioiron clearance and turnover. Increased erythropoesis leads to rapid removal of the isotope from plasma and the percentage utilization of the isotope for hemoglobin synthesis approaches 100%. However, if the patient has <u>increased</u> iron stores, the pattern is quite different. Since a greater amount of iron is present in the plasma and labile iron pool, the administered radioiron is diluted and the rate of transfer to red cell precursors in the marrow is reduced and plasma clearance prolonged. The slow uptake by the marrow allows a greater percentage to enter the iron stores, namely the liver[11]. This change in distribution causes a reduction in the per cent appearing in circulating cells. In spite of the slow plasma clearance, the total amount of iron leaving the plasma for the marrow and iron stores is increased to some 50 mgm./day. This chronic imbalance eventually produces signs and symptoms of hemochromotosis, the end-point of the process. Normal iron metabolism is schematically illustrated in Table II.

DEFINITION AND ETIOLOGY OF HEMOCHROMOTOSIS

Hemochromotosis is a clinical and pathological syndrome. Clinically, the common findings are pigmentation of the skin, cirrhosis of the liver, diabetes mellitus, endocrine dysfunction and heart failure. MacDonald and Mallory[20] contend (vigorously denied by others) that the diagnosis can only be made with certainty at the autopsy table and set forth their criteria for making the diagnosis. (1.) Cirrhosis of the liver of the "portal" type. (2.) Excessive iron deposits in hepatic parenchymal cells, in connective tissue and in bile duct epithelium. (3.) Pancreatic fibrosis and hemosiderosis. (4.) Parenchymal iron deposits in other organs of the body. In their analysis of 211 cases they found the average age of death to be 57 years; 91% affected were caucasian with 10:1 ratio of male to female; and there was no apparent connection with occupation. Of this group, 85% were heavy drinkers, 30% were affected with diabetes, 50% were asymptomatic and presented with pneumonia, neoplasm or heart failure. The most common cause of death was infectious disease. From these findings, they have suggested an entirely different pathogenesis [21,22,23,24]. They believe that this disease is simply a variant of nutritional cirrhosis in which abnormal absorption and deposition of iron is caused by the same dietary factors that lead to cirrhosis. MacDonald[25] has produced hemosiderosis in rats by feeding a choline deficient diet with increased iron.

The majority of investigators, however, look upon hemochromotosis as a genetic defect, inherited as an intermediate characteristic and its presence therefore depends on the presence of two

abnormal genes. Whether this defect manifests itself as a defect in the intestinal mucosa or as a result of increased tissue avidity for iron has not been determined. The contrasting theories are schematically represented in Table II. The fact that increased iron stores have been found in relatives of affected individuals is uncontested and fits nicely into the genetic theory.

Hemochromotosis is the result of gradual accumulation of storage iron in the range of 20-60 gm. The kinetics of normal and abnormal metabolism have been reviewed and are represented schematically on Tables III and IV[26].

DIAGNOSIS OF HEMOCHROMOTOSIS

The diagnosis rests upon the clinical findings plus determination of the SI, SIBC, bone marrow and liver biopsy. The Rous Test[27] for hemosideruria within epithelial cells is helpful. A more rapid test using intramuscular injection of 500 mgm. of Desferrioxamine has been used[28]. In this test, the urinary excretion of iron is measured six hours before and after injection. A 40-100 fold increase after injection of Desferrioxamine is indicative of iron overload.

TREATMENT OF HEMOCHROMOTOSIS

In order to control iron storage disease, a method of reducing total body iron must be instituted. If treatment to reduce iron storage is not employed, the resulting iron-induced fibrosis will cause progressive malfunction of the involved organs. Four

theraputic approaches are available[29]: (1.) Dietary restriction of iron, (2.) Chelating agents, (3.) Correction of primary disease, and (4.) Phlebotomy.

Dietary restriction of iron has little or no therapeutic effect as it decreases iron absorption by only a few milligrams daily. It may be helpful in preventing further accumulation of iron but has no effect on the iron already within the body.

The only chelating agent of therapeutic promise is Desferrioxamine B. IM injections of 500 mgm. twice a day will result in urinary excretion of 5-10 mgm. per day[30]. It is ineffective orally. Occasionally a patient may not respond. Additional disadvantages are expense and inconvenience. Its most useful application has been in the treatment of secondary hemochromotosis, acute iron toxicity and in patients with iron storage with associated refractory anemia[31].

Anemia directly or indirectly causes increased absorption of iron across the intestinal mucosa and if associated with ineffective utilization of iron in the erythrocytic series, results in excessive storage of iron in the body tissues. Anemia caused by deficiency of B_{12}, folic acid and pyridoxine may be "corrected" by the appropriate agent. Once the deficiency is corrected, the increased absorption and storage terminates.

The most efficient and effective method of removing body iron is by a systematic program of phlebotomy. A symptomatic patient may have a total body iron content of 20 to 50 gms. Each 500 ml. of blood withdrawn contains approximately 200-250 mgm. of iron. It is evident that 50 to 100 liters of blood must be drawn in

order to decrease the total body iron to within normal body limits and to prevent further damage. The management of the rapid phlebotomy method is still variable, however it is generally agreed that phlebotomy should continue until iron deficiency is manifest by (1.) subnormal mean corpustular hemoglobin concentration (MCHC), (2.) low serum iron, (3.) low saturated iron binding capacity (SIBC), and (4.) reticulocytopenia. At this point the labile iron store is depleted. Phlebotomy then continues at a slower pace until remaining stores are decreased to normal. Repeat hepatic biopsy is then indicated to determine iron content. Once iron stores are depleted, four to six maintenance phlebotomies are required per year to prevent accumulation of absorbed iron again. The reduction of iron is usually associated with ameloration of clinical symptoms and a return towards normal of specific tests of functions of involved organs. The degree of improvement, of course, depends on the amount of organ fibrosis present before treatment[29].

PHLEBOTOMY METHODS IN HEMOCHROMOTOSIS

The first recorded use of phlebotomy was by Hahn in 1942[34]. Massive long term phlebotomy was initiated by Howard, Balfour and Cullen[35] in 1947 and Finch[36] in 1948. In 1951 Beyers and Gitlow[37] reported a patient similarly treated. Davis and Arrowsmith[38] compiled 30 cases of hemochromotosis treated by venesection. The early attempts at this type of therapy was approached with extreme caution, with replacement of serum and a rather slow schedule, i.e. one phlebotomy per week. Myerson and Carrol[39] in 1955 reported a case in which 40 liters were removed in 28 months with good

clinical results, i.e. decrease in skin pigmentation, return of libido and amelioration of diabetes. Serial liver biopsies showed marked decrease in liver iron, but the fibrosis remained the same. The serum iron and SIBC returned to normal. McAllen, Coghill and Lubran [39] in 1957 reported six cases in which 500-1500 cc. were let per week.and reviewed extensively the British literature up to that time. Crosby[40] in 1958 reported a case in which 55 liters of blood were withdrawn in 11 months. During this time he found it is not necessary to reinfuse the patients protein, as the ability to produce plasma protein seemed to increase after the first few weeks of phlebotomy. Kimbrell[41] in 1962 reviewed the English literature and found 59 cases treated by multiple phlebotomy. In general, he found that phlebotomy results in an improved general well-being and lessening of skin pigmentation in almost all cases. Reduced liver size and improved liver function tests were seen in 79% of cases and more easily regulated diabetes in 61%. Failure of significant response to therapy can be anticipated in 20-25% and is usually seen in those cases with excessive fibrosis (Table VII). He also stated that reinfusion of plasma is not necessary if diet is adequate. Brody[42] and associated presented in 1962 there experience with six cases including one in which 45 L. were removed in three years. Duffy and Meister[43] presented a case in 1962 in which 108 phlebotomies (54 L.) were done in seven years. The response of their patient was favorable as compared to previous studies except that their patient showed little reduction in insulin requirement. The fact that the patient was viable after seven years is significant in that the former life-expectancy after diagnosis previous to venesection therapy was 4.4 years[44].

Insulin resistance in association with hemochromotosis has been reported on several occasions, as has failure to reduce insulin requirements during venesection. Hearth[45] in 1965 reviewed the literature and concluded that the insulin resistance that occurs in association with hemochromotosis is in no way related to the condition, and insulin resistance is probably no more liable to occur in diabetics with hemochromotosis than diabetics suffering from idiopathic diabetes mellitus. Corticosteroids may have a beneficial effect in this condition. Knauer et al[46] reported a case treated by 161 (80.5 L.) phlebotomies in six years that showed complete revision to normal of hemochromotic cirrhosis, diabetes and non-functioning gallbladder. This is the first reported case in which fibrosis of the liver was reversed. Liver fibrosis was previously considered to be permanent. This series of events suggests that the cirrhosis of hemochromotosis as well as the associated biochemical abnormalities are occasionally reversible. Williams[47] found that iron absorption increases during venesection and in some patients following completion of treatment, increases even further. This suggests that the primary defect is in absorptic

With our patient a regime of very rapid phlebotomy was attempte in a short time.

CASE REPORT

This 44 year old white chronic alcoholic was readmitted to Omaha Veterans Hospital on June 21, 1966, for re-evaluation of known hemochromotosis, diagnosed by liver biopsy in 1965. Laennec's cirrhosis was diagnosed in 1962 by liver biopsy and diabetes mellitu

by fasting blood sugar and glucose tolerance test in 1965. Since February, 1966, he had been taking 35 U Semilente and 100 U Lente insulin daily. The diabetes had been very difficult to control, the urine glucose varying from zero to four plus. Approximately eight years ago he apparently received an oral iron medication for an undetermined period of time for an "anemia", although the author was unable to document this. In 1965, the patient first noticed skin darkening, dark urine and ascites. Later he developed jaundice, and was hospitalized at OVAH. At this time liver biopsy and ferrokinetic studies revealed the presence of hemochromotosis. Thirteen phlebotomies were done. Repeat liver biopsies on June 28, 1965, and December 20, 1965, showed portal cirrhosis and presence of large amounts of iron pigment in hepatic cells.

Significant family history includes the fact that one brother, an abstainer from alcoholic beverage, has been shown to have an elevated serum iron and a liver biopsy showing increased iron pigment. One maternal uncle and two maternal aunts died of "cancer of the liver".

Physical examination was normal except for the following: bronzing of the exposed skin areas; spider nevi; facial telangietases, palmar erythema and gyne comastia. The abdomen was protruberant, the firm liver was palpable 8 cm. below the right costal margin and the spleen was palpable 6 cm. below the left costal margin. Ascites could not clearly be demonstrated.

Laboratory data on admission revealed normal values for CBC and UA. Prothrombin time was normal and coagulation time 19 min. Blood indices: MCV 92, MCH 31, MCHC 34. Reticulocyte count was 0.8%. FBS 203, BUN 10, SGOT 44, SGPT 15. Serum Fe was 193 and

SIBC was 209. Total bilirubin was 0.6. BSP 14% retention. Alkaline phosphatase 24, amylase 98, and lipase 0.8cc. Calcium 4.9 and phosphorus 4.3. EKG revealed anterior lateral ischemia. A chest film and UGI series were negative, although esophageal varicies were reported on x-ray in 1965. On July 6, Fe^{59} absorption was reported as 28.7 (N--20-30).

With this clinical picture it was decided to place the patient on a course of rapid, multiple phlebotomies[39], following his course with serial determinations for Hgb, hematocrit, reticulocyte count, SI, SIBC and TSP. (See Table I.) As much as 2500 cc. were removed per week and between June 22, 1966, and September 19, 1966, a total of 45 units were removed representing a volume of 22,500 cc. of blood. After removal of 16 units, the patient developed ankle edema and ascites, probably secondary to hypoalbuminemia and three units of salt free albumin were infused. Subsequently a method of autotransfusion was developed using the patient's own plasma. This, in conjunction with the use of Aldactone A, 50 mgm., and Hydrodiuril, 50 mgm. daily, easily controlled the edema although a small amount of ascites persisted. Due to low reticulocyte respons folic acid tid was begun on June 18, 1966, with good results.

On August 23, 1966, Ferrokinetic studies were repeated (see Table VI). Impression at this time was that the majority of the Fe^{59} went to marrow with no abnormal hepatic deposition. The Fe^{59} was rapidly cleared from the plasma and it was concluded that a functional iron deficiency existed in the circulating blood volume and no active deposition was seen in the liver. The stable Ht. suggested that the rate of new cell formation balanced removal and iron for new cell formation was arising from hepatic stores.

Phlebotomy was continued at a slower pace until September 15, 1966, at which time the laboratory studies indicated depletion of body iron stores, (Hgb. 7.3, Ht. 23, Retic. 8.4%, SI 21). The patient refused bone marrow examination. Due to persistant ascites, repeat liver biopsy was not attempted. The patient's diabetes continued to be brittle throughout the entire hospitalization in spite of careful management. During treatment, low values recorded include Hgb. 6.9, SI 16 and Ht. 21, but after ten phlebotomies the hemoglobin fluctuated between 7.5 and 9.9. The patient remained in the hospital one month following discontinuation of phlebotomy and during this period, vigorous diuretic therapy resulted in a 22 pound weight loss. Just prior to dismissal the hemoglobin was 9.8, Ht. 31, RBC 4,300,000, and Ret. 5.1. The SI was 22 and SIBC 243. This data, in conjunction with previous ferrokinetic studies, would indicate that mobilizable iron stores were depleted. The fact that bone marrow examination was refused and liver biopsy was unfeasible leaves to speculation whether liver stores were completely depleted. The patient was dismissed with medications including 120 U insulin, 100 mgm. Aldactone and 50 mgm. Hydroduiril daily.

FOLLOW-UP

The patient was readmitted on November 17, 1966, with a history of vomiting small amounts of blood and melena for two weeks. The patient had stomach cramps and discontinued his diuretics one week prior to admission. On admission he was quite dyspneic and had prominent ascites, liver palpable 12 cm. at right costal margin and a right pleural effusion. Admission hemoglobin was 6.9, Ht. 25,

and RBC 3,000,000. Right thoracentesis was done on November 19 and 2800 cc. of fluid was recovered. The patient experienced three episodes of hepatic coma in the next six weeks and blood ammonia leve were as high as 376 mgm.%. Each episode was treated in the usual manner. Due to persistant anemia, a 10 cc. test dose of Imferon was injected on December 9, 1966. It was felt that this procedure possibly would help determine the cause of anemia, as the clinical picture could have been either that of iron deficiency or toxic depression secondary to hepatic failure. The patient responded with an increase in RBC, Hgb., and Retic. On January 18, 1967, Hgb. 10.0, Ht. 34, RBC 4.25.and Retic. 2.8. The patient was dismissed on January 20 and medications included Neomycin, Lasix, Insulin and Multiple vitamins.

It is felt that this patient's hemochromotosis is under control although the cirrhosis and diabetes obviously continue to present problems. Phlebotomies done as primary therapy may favorably influence the cirrhotic process in the liver, although it is obvious that the patient's condition was diagnosed at a late stage in the natural history of the disease and complete reversal of the cirrhosis is therefore unlikely. This patient's prognosis is guarded, and much now depends on how faithfully he takes his medications and avoids noxious agents to prevent further hepatic decompensation.

DISCUSSION

Review of the English literature reveals that the treatment of choice for hemochromotosis is phlebotomy[38—47]. Crosby[39] in

1958 demonstrated that it is possible to let blood in large quantities with no adverse effects. On this basis we elected to phlebotomize our patient of large quantities in a short period of time. This was accomplished and a total of 22,500 cc. were let in less than three months, representing approximately 12 gms. of iron. A total of 60 phlebotomies was done in a year representing approximately 15 gms. of iron. The patient responded by an increased sense of well being. The insulin requirements decreased to 100 U. (20 U. Semi Lente and 80 U. Lente) daily. The bronze pigmentation decreased. The particular problems of this method, namely hypoalbuminemia and relatively depressed erythropoiesis reflected by a low reticulocyte count were easily managed with autotransfusion and folic acid. Other investigators, using a slower phlebotomy schedule had not encountered this problem.

CONCLUSION

It is possible to treat hemochromotosis with massive phlebotomy over a short period of time, provided that serial determinations of the patient's hematologic status are closely observed and tendency for hypoalbuminemia and reticulocytopenia are promptly managed. The status of the total body iron was not determined directly since liver biopsy and bone marrow could not be repeated, but available iron from storage was removed by this method.

TABLE I

Date	June 22	27	29	July 5	7	8	9	11
Hemoglobin	15.9			12.8		12.5		11.5
Hematocrit	48			41		40		36
Reticulocytes	.8					4.2		2.1
Serum Iron	193					116		
Serum Iron Binding Capacity	209					220		
Phlebotomy	X	X	X	X	X	X	X	X
Folic Acid tid								
Total Serum Protein	7.9					7.5		
Albumin	3.8					3.1		
Globulin	4.1					4.4		

Date	12	13	14	15	18	19	20	21
Hgb.			10.9	9.5	9.8	9.2	8.7	8.0
Ht.			30	30	30	29	26	24
Retic.			5.6	5.5	6.0		3.2	8.0
SI				129		114	94	78
SIBC				181				
Phleb.	X	X	X	X	X	X	X	X
Folic Acid tid					X		X	X
TSP					6.0			
A					2.8			
G					3.2			

Date	22	25	27	29	Aug. 1	2	3	4
Hgb.	8.0	9.0	9.5	9.1	9.2	9.2	8.5	8.0
Ht.	27	28	29	30	30	28	29	28
Retic.	9.9	8.5		3.7	13.2	10.1	9.5	7.3
SI	72	141		82	108	74	84	61
SIBC		236						
Phleb.	X			X	X	X	X	X
Folic Acid tid	X	X	X					
TSP		5.9			5.8			
A		2.5			2.7			
G		3.4			3.1			

Date	5	8	9	10	11	12	15	16
Hgb.	8.2		9.5	8.2	8.0	8.2	8.5	8.5
Ht.	26		28	28	23	29	29	28
Retic.	8.6		8.6	10.3	10.0	9.4	9.9	8.7
SI	70		56	58	79	62	78	76
SIBC								
Phleb.	X	X	X	X	X		X	X
Folic Acid tid				X	X			
TSP			6.3				6.1	
A							3.3	
G							2.8	

Date	17	18	24	26	29	30	31	Sept. 6
Hgb	8.2		9.2	9.0	10.3	7.3	7.1	8.2
Ht.	26		30	29	31	26	25	28
Retic.	10.2		7.1	5.0	3.1	6.0	6.1	9.2
SI	69		25	46	56	54	32	
SIBC			225					
Phleb.	X	X	X	X	X	X	X	X
Folic Acid tid							X	
TSP			6.4	6.9	6.5			
A			3.1	3.0	3.4			
G			3.3	3.9	3.1			

Date	7	8	9	10	12	13	14	15
Hgb.	7.2		7.3		7.3	6.9		7.3
Ht.	28		25		26	24		23
Retic.	7.1		8.2		6.4	8.7		8.4
SI	30		30		16	20	25	21
SIBC								
Phleb.	X	X	X	X	X	X	X	X
TSP					6.5			
A					3.0			
G					3.5			

Date	16	19	20	21	22	26	Oct. 3	Dismissed 14
Hgb.	6.9	6.0	6.9	7.0	7.1	8.0	9.0	9.8
Ht.	22	21	24		25	30	30	31
Retic.		7.8	7.6			3.4	1.4	
SI	15	24				28	24	20
SIBC								243
Phleb.								
TSP			6.7			7.3	7.5	
A			2.6			2.7	3.5	
G			4.1			4.6	4.0	

TABLE II

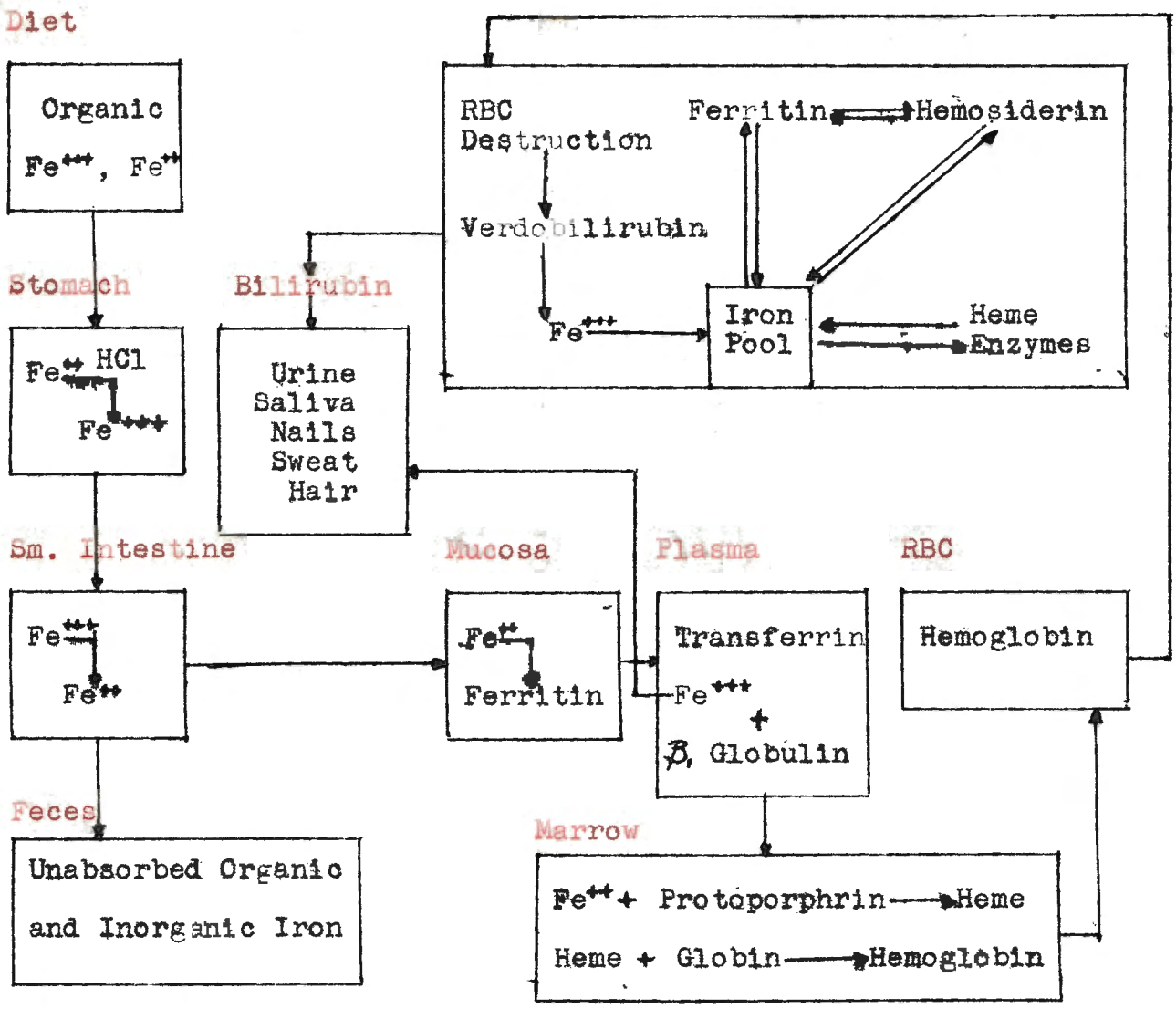

Diet
Organic
Fe+++, Fe++
Stomach
Fe++ HCl
Fe+++
Sm. Intestine
Fe+++
Fe++
Feces
Unabsorbed Organic
and Inorganic Iron
Bilirubin
Urine
Saliva
Nails
Sweat
Hair
RBC
Destruction
Verdobilirubin
Fe+++
Ferritin
Hemosiderin
Iron
Pool
Heme
Enzymes
Mucosa
Fe++
Ferritin
Plasma
Transferrin
Fe+++
+
β, Globulin
RBC
Hemoglobin
Marrow
Fe++ + Protoporphrin → Heme
Heme + Globin → Hemoglobin

TABLE III

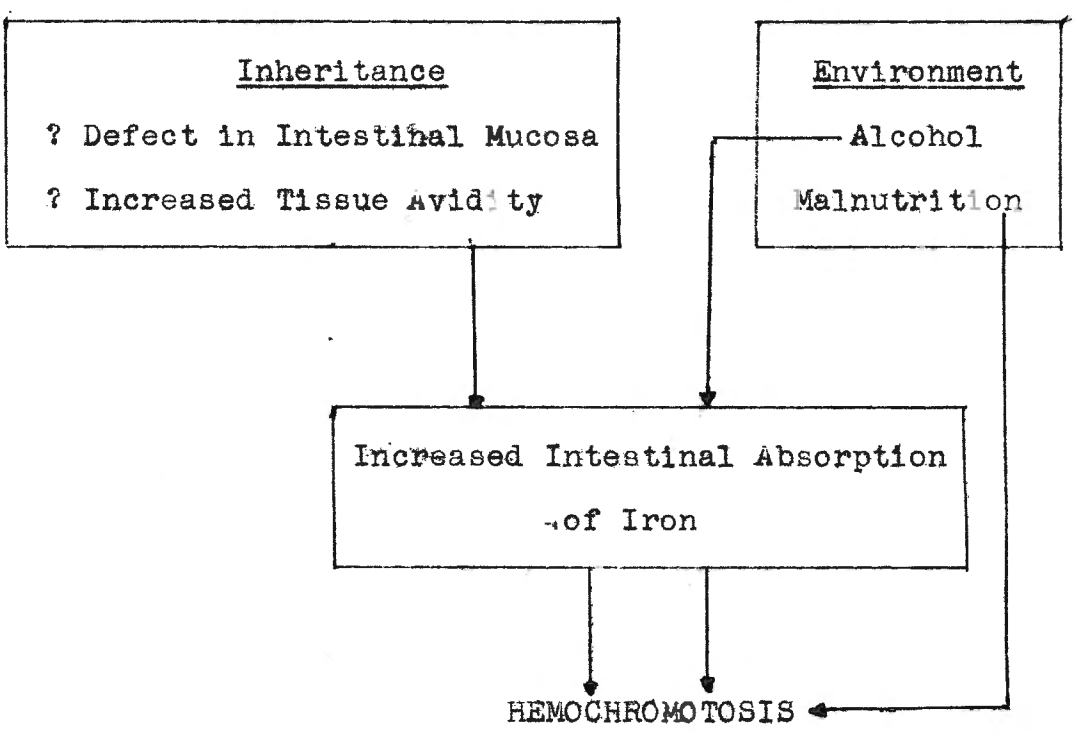
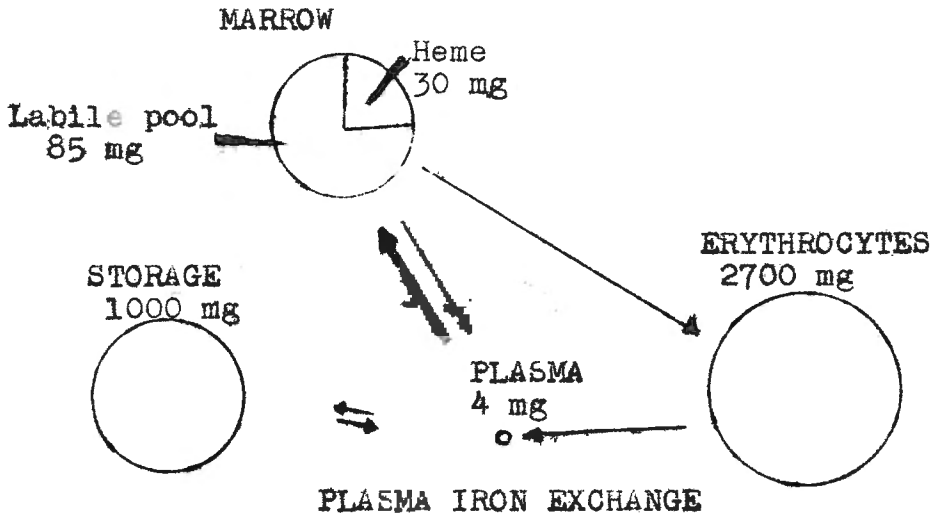

Inheritance
? Defect in Intestinal Mucosa
? Increased Tissue Avidity
Environment
Alcohol
Malnutrition
Increased Intestinal Absorption of Iron
HEMOCHROMOTOSIS

TABLE IV

NORMAL IRON KINETICS



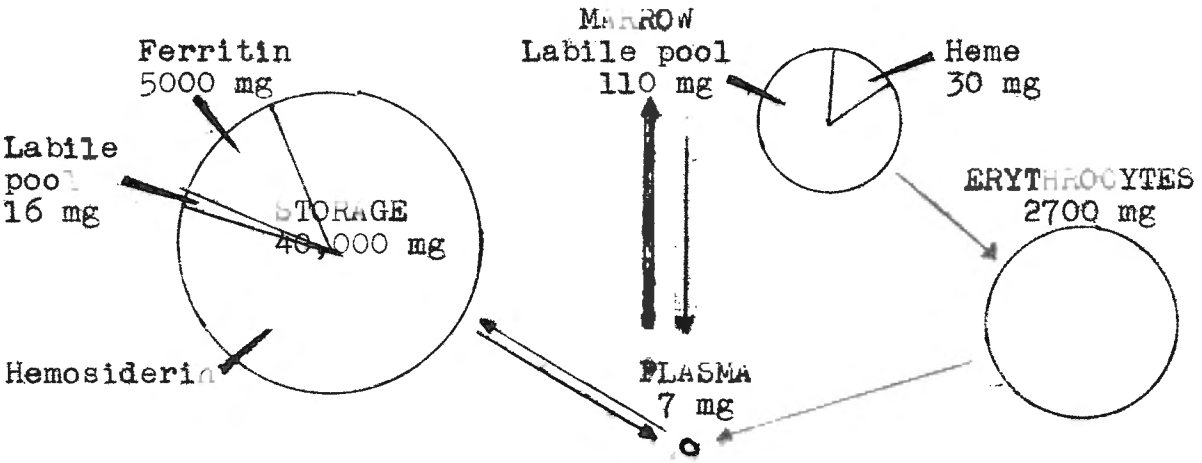
PLASMA IRON EXCHANGE

Total leaving plasma	35 mg/day
Erythropoietic labile pool	32
Storage	1
Extracellular fluid	1
Excretion and loss	1

Total entering plasma	35 mg/day
Erythrocytes	21
Storage	1
Extracellular fluid	1
Absorption	1
Erythropoietic labile pool	11

TABLE V

IRON KINETICS IN HEMOCHROMOTOSIS



PLASMA IRON EXCHANGE

Total leaving plasma	56 mg/day
Erythropoietic labile pool	32
Storage	20.5
Extracellular fluid	2
Excretion and loss	1.5

Total entering plasma	56 mg/day
Erythrocytes	21
Storage	18
Extracellular fluid	2
Absorption	4
Erythropoietic labile pool	11

TABLE VI

FERROKINETIC STUDIES

8—23—66

RBC Volume. . . . 1605 ml. . . or 19.2 ml./kg. . . . . (N—25—34)

Plasma Volume . . 4751 ml. . . or 58.6 ml./kg. . . . . (N—41 ± 1)

Serum Iron. . . . 136 mgm./100 ml.

Hematocrit. . . . 26-29

T ½ plasma Fe^{59} Clearance. . . 47 min. . . . . (N—60-120)

RBC Re-incorporation Fe^{59} Max. 64% in 7 days . . . . . (N— > 75%)

Organ Localization

(1) Sacrum: Counting rate increased rapidly to exceed twice time 0 in 2 hours with maximum of 2.5 in 4 hours. A rapid decline to 0 was seen in 4 days (N—slow decline to 0 in 10 days).

(2) Liver: All counting rates over liver were less than time 0.

Impression

The majority of the iron went to the marrow with no abnormal hepatic deposition. The rapid plasma clearance and rapid release from the marrow is compatible with an iron deficiency or hemolytic anemia. The rapid reincorporation is due to effective erythropoesis with autoutilization of iron, depleted by the multiple phlebotomies. Sufficient iron has been removed from the circulating hemoglobin so that a functional iron deficiency exists. The normal pattern over the liver suggests that it is not now the site of active iron deposition. The maintance of a stable hematocrit suggests the rate of new cell formation balances iron removal and iron for new cell formation is probably arising from hepatic stores.

11—22—66

RBC Volume. . . . 1197.5 ml. . . or 16.0 ml./kg. . . . (N—25—34)

Plasma Volume . . 5342 ml. . . or 71.2 ml./kg. . . . (N —41 1)

Total Blood Volume . . . . . 6539.5 ml. . . . or 57.2 mgm./kg.

12—20—66

Splenic Sequestration Studies negative in 20 days.

12—28—66

RBC Volume. . . . 1385 ml. . . . or 19.8 ml./kg.

Plasma Volume . . 5122 ml. . . . or 73.2 ml./kg.

TBV . . . . . 6507 ml. . . . or 93.0 ml./kg.

TABLE VII

SPECIFIC ORGAN IMPROVEMENT

Classification	Cases	Improved	Percentage
Skin Pigmentation	24	24	100
Hepatomegaly	24	19	79
Abnormal Liver Dysfunction	22	17	79
Diabetes Mellitus	22	14	61
Splenomegaly	5	5	100
Congestive Heart Failure	5	4	80
Decreased Libido	4	3	75
Myxedema	1	1	100

BIBLIOGRAPHY

1. Trousseau, A.: Clinique Medicale de l'Hotel Dieu de Paris. 2 nd Edition. London Bailliere, 1868.

2. Hanod, V. and Chauffard, A.: Cirrhose, Hypertrophique Pigmentaire dans le diabete sucre. Rev Med., Paris, 2: 385, 1882.

3. Sheldon, J. H.: Iron Content of Tissues in Hemochromotosis, with special reference to the brain. Quarterly Journal of Medicine. 21: 123, 1927.

4. Sheldon, J. H.: Hemochromotosis. London Oxford Univ. Press, 1935.

5. McCance, R. A. and Widdowsen, E. M.: Absorption and Excretion of Iron Following Oral and IV Administration. J.Physiology, 99:148, 1938.

6. Hahn, P. F., Bale, W. F., Ross, J. F., Balfour, W. M. and Whipple, G. H.: Radioactive Iron Absorption by the GI Tract; Influence of Anemia, Anoxia and Antecedent Feeding. Distribution in growing dogs. J. Expen. Med. 78: 168, 1943.

7. Conrad, M. E. and Crosby, W. H.: The Intestinal Mucosal Mechanism Controlling Iron Absorption. Blood, 22: 406, 1963.

8. Crosby, W. H.: The Control of Iron Balance by the Intestinal Mucosa. Blood, 22: 441, 1963.

9. MacDonald, R. A.: Idiopathic Hemochromotosis--Genetic ir Acquired. Arch. Int. Med., 112: 184, 1963.

10. Finch, S. C. and Finch, C. A.: Idiopathic Hemochromotosis, an Iron Storage Disease, Iron Metabolism in Hemochromotosis. Medicine, 34: 381, 1955.

11. Polygrove, M. and Mortimer: The Quantitative Determination of Iron Kinetics and Hemoglobin Synthesis in Human Subjects. J. Clinical Invest. 40: 753, 1961.

12. Moore, C. V., Dubach, R. V., Minnich, J., and Roberts, H. K.: Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and Dogs; J. Clinic. Invest. 23: 755, 1944.

13. Williams, R. and Pitcher, C. S., Iron Metabolism and the Liver with particular reference to the pathogenesis of hemochromotosis, Post. Grad. Med. Journal, 39: 193, 1963.

14. Smith, M. D., and Pannaciulli, I. M.: Absorption of Inorganic Iron from Graded Doses. Brit. Journ. Hemat. 4: 428, 1958.

15. Biggs, J., Bannerman, R. and Gallender, S. T.: Iron Absorption in Achlorhydria. Proc. 8th Congr. Europ. Soc. Hemat., Vienna, p. 236, 1961.

16. Granick, S.: Protein, Apoferritin and Ferritin in Iron Feeding and Absorption. Science; 103: 107, 1946.

17. Wohler, F., Heilmeyer, L., Ehrich, D. and Kang, S.: Zun Function des Ferritins bei der Eisenresoption: Arch. erp Rath. Pharak, 203: 107, 1957.

18. Pirzio--Biroli, G., Bilhwell, T. H. and Firch, C. A.: Iron Absorption of Radioiron Administered with a Standard Test Meal in Man. J. Lab. Clin. Med. 51: 37, 1958.

19. Laurell, C. B.: Iron Transportation: Iron in Clinical Medicine, p. 8, 1958.

20. MacDonald, R. A. and Mallory, G. K.: Hemochromotosis and Hemosidenosis. AMA Arch. Int. Med. 105: 686, May, 1960.

21. Techet, G. S. and MacDonald, R. A.: Idiopathic Hemosidenosis. New Eng. J. Med. 267: 6, July, 1962.

22. MacDonald, R. A.: Idiopathic Hemochromotosis. Arch. of Int. Med. 107: 606, 1961.

23. MacDonald, R. A.: Idiopathic Hemochromotosis, Genetic or Acquired: Arch. Int. Med. 112: 184, 1963.

24. Hemochromotosis. Genetic or Acquired: The Lancet. 4: 750, 1966

25. MacDonald, R. A.: Experimental Rigment Cirrhosis, Am. J. Rath. 36: 499, 1960.

26. Pollycove, M.: The Metabolic Basis of Inherited Disease: Chapter 34; 780-810, 2nd Ed., McGraw-Hill Co., New York, 1966.

27. Rous, P.: Urinary Siderosis, J. Exp. Med., 28: 645, 1918.

28. Keberle, H.: Iron Metabolism, edit. by F. Gross, p. 600. Springen, Berlin, 1964.

29. Duncan, T. G.: Med. Clinics of North America, 49: 1367, 1965.

30. Wohler, F.: The treatment of Hemochromotosis with Dexferrioxamine. Acta. Hematology, 30: 65, 1963.

31. Moeschlin, S. and Schniden, U.: Treatment of Primary and Secondary Hemochromotosis and Acute Iron Poisoning with a New, Potent Iron Eliminating Agent (Dexferrioxamine-B). Iron Metabolism, Edit. by F. Gross, p. 525, Springer, Berlin, 1964.

32. Adams, W. S., Leslie, A. and Levine, M. H.: Proc. Soc. Exp. Biology (N. Y.) 74: 46, 1950.

33. Haskins, D., Stevens, A. R., Finch, S. and Finch, C. A.: J. Clinical Investigation, 31: 543, 1952.

34. Balfour, W. M., Hahn, P. F., Bale, W. F., Pomnecenke, W. T. and Whipple, C. H.: Radioiron Absorption in Clinical Conditions: Normal, Pregnancy, Anemia and Hemochromotosis. J. Expen. Med. 76: 15, 1942.

35. Howard, R. B., Balfour, W. M. and Cullen, R.: Hemochromotosis with Notes on Treatment of one patient by means of repeated venesections, J. Lab. and Clin. Med. 43: 848, 1954.

36. Finch, C. A. and Finch, S.: Iron Metabolism and the Pathophysiology of Iron Storage, Blood, 5: 983, 1950.

37. Beyers, M. R. and Gitlow, S. E.: Metabolism of Iron in Hemochromotosis. Am. J. Clin. Path. 21: 349, 1951.

38. Davis, W. P. Jr. and Arrowsmith, W. R.: The treatment of Hemochromotosis by Massive Venesection, Ann. Int. Med. 39: 723, 1953.

39. McAllen, P. M., Coghill, N. F. and Lubran, M.: The Treatment of Hemochromotosis with particular reference to removal of iron from the body by repeated venesection, Quart J. Medicine, 102: 251, 1957.

40. Crosby, W. H.: Treatment of Hemochromotosis by Energetic Phlebotomy. One patient's response to the letting of 55 L. of blood in eleven months. British J. of Hemo. 4: 82, 1958.

41. Kimbrell, O. C.: Hemochromotosis: Review of Therapy and Report of a New Case, No. Carol. Med. J. 23: 280, 1963.

42. Brody, J. I., McKenzie, D. and Kimball, S. G.: Therapeutic Phlebotomies in Idiopathic Hemochromotosis, Am. J. Med. Sciences, 244: 575, 1962.

43. Duffy, T. J. and Meister, C.: Hemochromotosis--a report of a case followed for seven years with repeated phlebotomies and liver biopsies, Am. J. Med. 25: 435, 1962.

44. Finch, S. C. and Finch, C. A.: Idiopathic Hemochromotosis, an Iron Storage Disease, Medicine, 34: 381, 1955.

45. Heath, M. B.: Insulin Resistant Diabetes Mellitus in Association with Hemochromotosis. Post. Grad. Med. J. 41: 560, 1965.

46. Knauer, C. M., Gamble, C. N. and Monroe, C. S.: The Reversal of Hemochromototic Cirrhosis by Multiple Phlebotomies, Gastroenterology 49: 667, 1965.

47. Williams, R., Manenti, F., Williams, H. S. and Pitcher, C. S.: Iron Absorption in Idiopathic Hemochromotosis before, during and after Venesection Therapy, Brit. Med. J. 2: 78, 1966.