Secondary Hemochromatosis

I. Transfusion (Exogenous) Hemochromatosis

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HEMOCROMATOSIS ("bronzed diabetes") is a condition of unknown etiology in which the body iron stores are vastly increased and in which there is portal cirrhosis of the liver. Diabetes, pigmentation of the skin, and pancreatic fibrosis are frequently, though not invariably, present. Numerous blood transfusions in certain patients have resulted in the production of a condition clinically somewhat similar to hemochromatosis. These two conditions have been separated by terming the former, idiopathic type "endogenous" (since the increased iron in the body has been absorbed through the gastrointestinal tract) while the latter, transfusion type has been called "exogenous."

The literature contains about twenty cases \textsuperscript{1-4, 18-21} which have been presented as examples of the exogenous type. The purpose of this paper is to review these cases critically, point out serious deficiencies in the present concept of exogenous hemochromatosis, contribute two more cases, and postulate a possible etiology.

Case Reports

Case 1

E. P., a 58 year old white male, entered the hospital on July 25, 1949, because of weakness and fatigue, fever, and weight loss of two months duration. Prior to admission he had received four blood transfusions and oral iron therapy. The patient had had inguinal herniorrhaphies in 1930, pneumonia in 1940, and chronic idiopathic pneumonitis in 1942; on each of these occasions the hemoglobin was 14 Gm. per 100 ml. and the leukocyte counts and morphology were normal. In December 1941, prior to repeat herniorrhaphies, the hemoglobin was 12 Gm. per 100 ml. and the leukocyte count 3900 per cu. mm., with 44 per cent neutrophils, 52 per cent lymphocytes, and 3 per cent monocytes. In August 1946, when admitted because of a fracture of the os calcis, the leukocyte picture was unchanged but the hemoglobin was 10.5 Gm. per 100 ml.

On physical examination the patient appeared pale, the liver edge was felt 2 cm. below the right costal margin, and the spleen was barely palpable. The oral temperature was 100.6 F., the pulse rate 100 per minute, and the blood pressure 100 mm. Hg systolic and 60 mm. Hg diastolic.

Laboratory studies revealed the hemoglobin to be 6.6 Gm. per 100 ml., the leukocyte count 2200 per cu. mm., and the differential count as follows: 52 per cent neutrophils (30 per cent mature, 4 per cent metamyelocytes, 2 per cent myelocytes, 14 per cent promyelocytes, and 2 per cent blast forms), 32 per cent lymphocytes, 7 per cent eosinophils, and 7 per cent basophils. Similar determinations made throughout his illness showed comparable values. The platelet count was 20,800 per cu. mm. The erythrocytes showed polychromasia, hypochromasia, and poikilocytosis. Nucleated red cells were reported in
varying numbers, from 2 to "many." The percentage of reticulocytes varied between 1.0 and 0.1 per cent. The bone marrow was very hypercellular due to a marked increase in the myeloid series. This series contained definitely increased numbers of immature cells including a moderate increase in the myeloblasts. The basophils were greatly increased in numbers, both relatively and absolutely. The urine sediment contained up to 100 erythrocytes per high power field. Gastric analysis showed 32 degrees free HCl. Four stool specimens were negative for blood, ova, and parasites. Renal function studies were normal. The serum bilirubin was 0.2 mg. per 100 ml. in 1 minute and 0.3 total. The fecal Ehrlich's test showed 480 units per 100 Gm. X-ray examinations of the chest, skull, and long bones were negative.

Therapy consisted of a nutritious diet and blood transfusions. Irradiation was never employed.

The patient was hospitalized on fifteen subsequent occasions. Throughout the course of his illness, his hemoglobin fell on many occasions to between 4.7 and 7.5 Gm. per 100 ml., despite transfusion therapy. On March 1, 1950, splenectomy was performed, the specimen weighing 375 Gm.; except for improvement in his platelet count which lasted until March 1951, this procedure did not produce any significant effect. Until May 1951, sufficient blood transfusions were repeatedly given to raise the hemoglobin to 12 or 13 Gm. per 100 ml. Thereafter, because of increasing difficulty in preserving his veins, transfusions were usually given sufficient to raise the hemoglobin to 9.5 or 10.5 Gm. per 100 ml.

Eight months after transfusion therapy had been begun, during which time the patient received 40 pints of blood, the fasting blood glucose was 78 mg. per 100 ml. Six weeks later, following eight more transfusions, an oral glucose tolerance test gave the following result: fasting 90; 30 minutes 140; 1 hour 144; 2 hours 101; and 3 hours 94 mg. per 100 ml.; there was no glycosuria. At this time a skin biopsy showed few granules of iron-staining material around the sweat glands and in the interstitial cells of the upper corium. The retention of sulfobromophthalein was 11 per cent 45 minutes after injection of 5 mg. of dye per Kg. body weight; the thymol turbidity was 10.7 units, the serum bilirubin 0.2 mg. per 100 ml. in 1 minute and 0.6 total, the prothrombin activity 60 per cent, cephalin cholesterol flocculation 1 plus, serum albumin 3.9 Gm. per 100 ml., and serum globulin 3.0 Gm. per 100 ml. The erythrocyte fragility test and three Coombs tests were negative. In June 1950, the patient had acute pyelonephritis due to E. coli. The acute episode responded to antibiotic therapy, but subsequent examinations continued to show evidence of chronic pyelonephritis due to the same organism, and the patient's course was punctuated by episodes of acute epididymitis and acute prostatitis. Aureomycin and terramycin were given repeatedly for long periods in an attempt to control these complications. On July 17, 1950, the serum iron was noted to be "markedly elevated," and the iron binding capacity of the serum was 0. To date, the patient had received 58 pints of blood. An oral glucose tolerance test gave the following result: fasting 90; 30 minutes 154; 1 hour 178; 2 hours 172; and 3 hours 147 mg. per 100 ml.; glycosuria was found at 1, 2, and 3 hours. Throughout the patient's entire illness, however, multiple routine urinalyses failed to show glycosuria. Progressive bronzing of the skin was noted. Several episodes of thrombophlebitis, two dental abscesses and an episode of acute laryngitis all responded to therapy. On May 14, 1951, a four day collection of the feces revealed excretion of 400 mg. of urobilinogen per 24 hours. In July, 1951, following 90 blood transfusions, the liver edge was 5 cm. below the costal margin. The fasting blood sugar was 95 mg. per 100 ml., and two subsequent determinations were normal. The blood urea nitrogen was 15 mg. per 100 ml. on October 12, 1951, after which no such determination was again made.

The patient's final hospitalization, which began May 1, 1952, was marked by continued progression of weakness, weight loss, and by frequent episodes of chills and fever. Although some five of the latter episodes occurred following blood transfusions, neither hemoglobinemia nor hemoglobinuria were at any time demonstrable. Blood cultures were negative, as were indirect Coombs tests against the donor cells. The skin was remarkably bronzed. Pains in the chest, abdomen, and joints became manifest, and a small pleural effusion was noted on the left. After three months of unmanageable spiking fever, progressive deterioration, and a terminal hemorrhagic diathesis, patient expired on September
7, 1952, at the age of 61. He had received one hundred sixty transfusions of blood (80 liters) during the thirty-nine month course of his illness.

**Necropsy findings. Gross:** The cause of death was found to be massive gastrointestinal hemorrhage associated with a generalized hemorrhagic diathesis. Petechiae, ecchymoses,

and small hemorrhages were found in the kidneys, lungs, skin, thyroid, and other organs. There was moderate coronary arteriosclerosis, diffuse myocardial fibrosis, and moderate pulmonary edema. The spleen was surgically absent. The liver weighed 2350 Gm., was mahogany reddish brown, and showed a fine granularity on cut section. Three separate,
soft, white, sharply circumscribed nodules, each 1 cm. in diameter, were present in the.

The color of the pancreas was the same as that of the liver. Lymph nodes were not.

remarkable. Microscopic: The epithelial cells of almost every organ examined contained

hemosiderin, and even the myocardial fibers were heavily laden with this pigment.

Extensive deposits of hemosiderin in the liver were present in the parenchymal cells, the

ton Kupffer cells, and in macrophages clustered in the portal areas. The latter were greatly

enlarged as a result of a fibrotic process which had produced intercommunication of portal

Fig. 2.—(a) Liver from case 1. Hemosiderin is demonstrated as large black masses in

the edge of a portal area and as smaller, diffusely scattered deposits within liver cord

cells. × 210. Prussian blue. (b) Pancreas from case 1. Interstitial fibrosis is apparent.

× 25. Hematoxylin and eosin.
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Areas and distortion of the hepatic architecture. Central veins, where present at all, had been forced into an eccentric position in the lobule. The soft white nodules in the liver were partially necrotic leukemia infiltrates. Moderate fibrosis was present in the pancreas, with hemosiderin deposition prominent in the acinar tissue and to a lesser extent in the islets; Gomori stains revealed greatly decreased quantities of beta granules in the islet cells. Myeloid cells, most of which contained round nuclei, were found to have replaced all other elements of the bone marrow, including fat. The spleen, which had been removed two and one-half years before death, showed a markedly increased content of hemosiderin scattered in the form of small granules within the reticuloendothelial cells; a few small foci of myeloid metaplasia were present, but no remarkable morphologic abnormalities were otherwise apparent. Final diagnoses included: chronic myelogenous leukemia; hemochromatosis of the liver (siderotic cirrhosis); hemosiderosis and fibrosis of the pancreas; hemosiderosis of the bone marrow, lymph nodes, heart, skin and all body epithelium; diabetes mellitus.

Case 2

C. A. A., a 65 year old white male, had onset of weakness in 1942 and he was found to be anemic in November 1943. Therapy with liver and iron was ineffective. There was a history of careless use of various insecticides for eighteen years. On his first admission to the hospital, which was in January 1944, examination of the patient revealed only pallor and a few petechiae. The hemoglobin was 4.1 Gm. per 100 ml., the hematocrit 13.5 per cent, the erythrocyte count 1,300,000, the leukocyte count 4,000 with 49 per cent neutrophils and 49 per cent lymphocytes, the platelet count 145,000 and the reticulocyte percentage 1.4. The erythrocytes were macrocytic. Free HCl was present in the stomach aspirate. Bone marrow study resulted in the diagnosis of refractory anemia, and blood transfusions were given repeatedly thereafter. In November, 1944, the hemoglobin was 4 Gm., the leukocyte count 3,150 with 25 per cent neutrophils and 74 per cent lymphocytes, the MCV 144 cu. μ, the MCH 38 μg., and the MCHC 27 per cent. Roentgenogram of the chest showed cardiac enlargement. Folic acid therapy produced no response. In December 1945, the liver became palpable. Folic acid therapy was again ineffective. In and prior to April 1946, urinalyses showed no glycosuria. In June 1946, skin pigmentation became manifest and increased progressively thereafter. Weight loss, polydipsia, and polyuria began in 1948 and became severe in September of that year. At that time, the skin pigmentation was generalized and intense, the liver edge was palpable 3 fingerbreadths below the right costal margin, and there was auricular fibrillation. There was 4 plus glycosuria, the blood sugar was 555 mg. per 100 ml., and the CO₂ was 56 vol. per cent. There was 12 per cent retention of sulfobromophthalein 45 minutes after injection of 5 mg. of the dye per Kg. of body weight. A liver biopsy revealed hemochromatosis, and a skin biopsy showed dermal deposition of melanin and a small amount of iron. Insulin therapy was required for control of the patient's diabetes, and the cardiac rhythm became regular following a short course of treatment with quinidine sulfate. The patient's hemoglobin in September 1948, was 7.6 Gm. per 100 ml., the leukocyte count 2,700 with 54 per cent neutrophils and 38 per cent lymphocytes, and the Roux test for hemosiderinuria was positive. He expired at a rest home on October 25, 1948. Throughout the course of his illness, the patient had received one hundred ninety-one blood transfusions, approximately 500 ml. each. Short-lived transfusion reactions had occurred on about twelve occasions, manifested by mild chills and low-grade fever.

Necropsy findings. Gross: Intense brown pigmentation of the skin was present over the entire body. One thousand cubic centimeters of clear yellow fluid were present in the abdominal cavity. The heart weighed 500 Gm. and the myocondium was reddish-brown. The spleen weighed 130 Gm. and except for mild perisplenitis did not appear remarkable. The liver weighed 2,200 Gm. and was deep brown in color, as was the pancreas. No other significant findings were apparent in the remainder of the organs. Microscopic: Extensive
hemosiderosis of the myocardium was found. The pancreas contained hemosiderin granules in abundance in the acinar tissue, to a lesser extent in the islet tissue. The phagocytic cells of the spleen also contained increased quantities of hemosiderin, as did the epithelial cells of the prostate, gall bladder, adrenal and distal convoluted tubules of the kidney. The liver showed a marked increase in portal connective tissue with intercommunicating portal areas. Architectural distortion was marked, and large quantities of hemosiderin

Fig. 3.—Liver from case 2 (C. A. A.). Hepatic cirrhosis is manifested by enlarged, fibrotic, intercommunicating portal areas resulting in gross destruction of liver architecture. × 30. Hematoxylin and eosin.
were apparent within liver cells, von Kupffer cells, and portal connective tissue. Final diagnoses included: Primary refractory anemia; hemochromatosis of the liver (siderotic cirrhosis); hemosiderosis and fibrosis of the pancreas; hemosiderosis of the heart, skin and all body epithelium; diabetes mellitus.

Fig. 4.—(a) Liver from case 2. Hepatic parenchyma is not counterstained; all black-staining material is hemosiderin. X 22. Prussian blue. (b) Pancreas from case 2, showing interstitial fibrosis. X 35. Hematoxylin and eosin.

**Discussion**

*What is Exogenous Hemochromatosis?*

Interest in this problem is not particularly a therapeutic one; individuals with this condition usually have a serious disease which demands repeated blood
transfusions. Nevertheless, such cases may provide valuable contributions toward discovery of the etiology of cirrhosis and diabetes.

Much of the confusion in the concept of this condition arises from a failure to differentiate between hemosiderosis and hemochromatosis. In hemochromatosis the iron content of the entire body is increased and is, by definition, invariably accompanied by cirrhosis of the liver. Hemosiderosis, on the other hand, merely means that a particular tissue (or the entire body) contains more iron than is normally found there; it does not in any way imply altered function or morphology in such tissue. It is vital to keep this difference in mind for the simple reason that since the body has no known effective method of excreting iron other than by hemorrhage, once iron is introduced into the body it must remain there. Thus, if iron is injected into the body in the form of transfusions, after death of the red cells it must necessarily be deposited in various organs of the body, and it is therefore not surprising to find it still present at autopsy. Only when such deposits are accompanied by functional or morphologic alteration of these organs does the condition become of interest. It follows, then, that mere deposition of iron in an otherwise normal organ is simple hemosiderosis. An example of such a process is the increased iron content of the liver in many cases of hemolytic anemias; the liver in these cases is otherwise normal.

In endogenous hemochromatosis, on the other hand, not only is the iron content of the liver and the body as a whole vastly increased, but portal cirrhosis invariably exists with all its clinical and morphologic manifestations. If we are to draw an analogy for the pursuit of basic research between the condition produced by multiple transfusions and that which we term “endogenous hemochromatosis”, it is imperative that the features invariably present in the one also be present in the other. Endogenous hemochromatosis has only two consistent features, increased total body iron and portal cirrhosis. Diabetes may be absent in as many as one third of the cases, and the pigmented skin is merely another tissue in which iron has been deposited and which happens to be located in a site where it is clinically obvious. In any one case, therefore, we are compelled to insist only upon increased body iron and cirrhosis as the criteria also for the exogenous form. Increased body iron is usual, and the result of transfusion. Whether or not cirrhosis is present becomes of critical significance, and it is with this point in mind that cases in the literature were reviewed. It may be mentioned here that mere “mild portal fibrosis” or equivalent terms are difficult to evaluate. Certainly they may constitute a very early stage of portal cirrhosis and it is to be expected that a large series of cases would show a number of examples of this type representing the transition stages between normal livers and those with advanced cirrhosis. Mild nonspecific portal fibrosis, however, may be present in other conditions. If the end result of exogenous hemochromatosis is to be accepted as being identical with that of the endogenous form, one would expect the group of cases of the exogenous type to include a convincing number with unequivocal portal cirrhosis. The following review shows that surprisingly few such cases have been reported.

Critical Review of Previously Reported Cases

In 1937 Kark reported a patient with aplastic anemia who received over two hundred ninety transfusions before death and who developed pigmentation of
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the skin, enlarged liver, and possibly diabetes. Unfortunately the liver was not biopsied nor was an autopsy done. Humphreys and Southworth described a palpably enlarged liver, but did not state whether or not the liver was cirrhotic at autopsy. Their patient died with sudden jaundice and coma, but it is not clear whether this was the result of acute hepatic necrosis or cirrhosis. In their cases nos. 3, 38, and 39, Bomford and Rhoads (being concerned with other aspects of the problem) referred to the liver only in passing and described it as showing “early portal fibrosis” or “early multilobular fibrosis.” No illustrations of these livers accompany the article. It is difficult, therefore, to be sure that these descriptions represent cirrhosis. Norris and McEwen report their case as an example of exogenous hemochromatosis, but state that the liver was not cirrhotic. Mackey describes his case as showing a cirrhotic liver; no illustrations are submitted but the description is plausible. The description of the liver in Chesner’s case would lead one to believe it was cirrhotic but the illustration is equivocal. The case also is odd in that, although large amounts of iron were present at autopsy, the patient received only about twelve transfusions. The description and photomicrograph of the liver in Zeltmacher and Bevans’ case, although not completely convincing, are reasonably plausible. Finch’s case, although not reported in detail, appears acceptable in every way, and the photomicrograph shows an obvious cirrhosis. Case 5 of Muirhead et al. is not illustrated but their description leaves little doubt about the presence of cirrhosis; the case, however, presents features very similar to that of Chesner and is discussed below. Case 3 of Wyatt’s 1949 report is referred to by the author as “cirrhotic” but no illustrations are offered and the description is inadequate for evaluation. Case 7 in his 1950 report falls in the same classification. The author cites case 8 as one resembling that of Kark, but again no means of evaluating the liver changes are offered other than the statement that the microscopic picture was that of “siderotic cirrhosis.” The remainder of Muirhead’s and Wyatt’s cases showed no cirrhosis. We are left with the five cases reported by Schwartz and Blumenthal. Cases 1, 2, 4, and 5 are all illustrated but most pathologists would not feel that the very mild fibrosis in these photomicrographs represents definite cirrhosis. Case 3 is not illustrated, no autopsy was done, and the liver biopsy showed “early portal cirrhosis.” It is regrettable that case 5 was not better illustrated since the liver weighed 3160 Gm. and was described as “markedly fibrotic.”

We feel that exogenous hemochromatosis as defined above does exist, and we offer two case reports as examples. We also believe that several of the previously reported cases (Zeltmacher and Bevans, Finch, case 5 of Schwartz and Blumenthal, and Mackey) are probably examples of this condition, but that the lack of adequate documentation has taken much of their value from these cases when the very existence of the entity is being questioned.

Iron Metabolism

One feature of the reported cases has been disturbing. At first it was assumed that all of the iron present in these cases had been introduced by means of blood transfusions. Actual analysis of the organs, however, has revealed that some of the cases contained more iron in the liver alone than was accounted for by trans-
fusion. Chesner's case is the extreme example, a 14 year old boy who had had a hypochromic microcytic anemia for at least six years. Transfusions accounted for only 2.75 Gm. of iron, yet 47 Gm. were present in the liver alone. Further examples of this discrepancy are cited by Muirhead and Wyatt. In order to evaluate this, a brief outline of iron metabolism is presented.

The body contains no known effective way of eliminating iron other than through hemorrhage. Thus, once absorbed, iron cannot normally leave the body in significant quantities. Under normal conditions, probably only about 1 mg. per day or less of ingested iron is absorbed; this amount is known to be increased in patients who are iron deficient. Although varying results have been obtained, it is apparently also increased in endogenous hemochromatosis. The actual mechanism which regulates iron absorption from the gut has never been definitely established. Granick proposes a "mucosal block" theory in which the protein, apoferritin, is formed in the intestinal mucosal cell and combines with ferrous iron from the gut to form ferritin, releasing the iron to the blood only when the body needs it. The iron in the blood combines with a blood protein, "siderophillin," which carries it to the tissues. Release of the iron to the blood converts the mucosal ferritin to apoferritin which then breaks down, being resynthesized when further passage of iron into the cell occurs. Body iron stores apparently determine when ferritin will release its iron to the blood. Thus, if body stores are adequate, apoferritin in the intestinal mucosa becomes saturated with iron, blocking further absorption of iron from the gut. According to Granick this is the normal mechanism of regulation, and Gillman et al. attempted to demonstrate this morphologically. Experimentally, this mechanism can apparently be bypassed by massive doses of iron, low phosphorus intake, or both. Body iron stores may normally express their need for iron through the degree of saturation of siderophillin in the blood, but, at least in disease conditions, this appears to be an inadequate explanation as was pointed out by Granick. Anoxia from anemia has also been postulated as regulating the degree of apoferritin saturation. The iron is carried from the intestinal mucosa through the blood to the spleen, liver, and marrow. The former two organs (through an apoferritin-ferritin system of their own) serve as body stores, shunting their iron to the marrow as it needs it for building hemoglobin.

Etiology

The etiology of hemochromatosis in general is unknown. It has usually been accepted that the absorption regulating mechanism ("mucosal block") of the intestinal mucosa is faulty, allowing increased quantities of iron to enter the body daily, and that the presence of this iron in some way produces local injury in the liver and pancreas leading to cirrhosis, pancreatic fibrosis, and diabetes. That the iron is locally toxic has been challenged by the failure to reproduce the phenomenon experimentally in animals. Zeltmacher and Bevans, speaking of aplastic anemia, stated that they believed some toxin injured both the liver and bone marrow and that the increased iron absorption merely occurred as a consequence of the anemia, the iron having no local toxic effect. Gillman and Gillman, on the other hand, found cirrhosis and increased iron absorption occurring in South African natives who were on a corn-grit diet and developed
PELLAGRA. This diet has been found to be high in iron content and a similar diet, used experimentally, has been found to be low in phosphorus. Finch performed experimental studies and showed that low phosphorus diets enhanced iron absorption in animals, particularly if the iron content of the diet was increased.

Since the quantity of iron present in many cases of exogenous hemochromatosis exceeds that which was introduced through blood transfusions, it is apparent that these patients must have absorbed the difference through the gastrointestinal tract. In attempting to apply the above mentioned mechanisms, it is possible to postulate an explanation of this phenomenon without discarding Granick's "mucosal block" concept. There is a single common denominator in the basic disease of all reported cases; this factor is anemia. Various types are represented: aplastic or refractory, hypochromic microcytic, "erythroid maturational arrest," and the anemia of uremia. It is thus apparent that many anemic patients continue to absorb iron, whether they need it or not. Actual measurement by means of radioactive isotopes has shown that some anemic patients continue to absorb appreciable quantities of iron. If such a patient has a continuous anemia for a long period of time, it is theoretically possible for him to absorb large quantities of iron and develop hemochromatosis even without transfusions. We are publishing such a case in detail in a separate report. In most instances such patients will not live long enough to develop cirrhosis, and in these cases autopsy reveals varying degrees of simple hemosiderosis. Iron added by transfusions probably merely accelerates a process already in progress.

From a therapeutic point of view there is an implication in the above deductions. Chesner's case of a 14 year old boy bears this out most dramatically. The normal American diet contains 10 to 15 mg. iron per day and normally less than 1 mg. is absorbed. Even if this patient absorbed 10 mg. per day from his diet throughout his entire life (and it is unlikely he took in this much during the first few years of life), this, together with 2.75 Gm. which were transfused, would account for only about 54 Gm. Yet the liver alone in that case contained 47 Gm. and in view of the large quantities present in the spleen and other organs, it is safe to assume that much more than this was present at autopsy in the entire body. The additional iron could only have come from iron therapeutically administered by mouth. It is therefore quite possible that prolonged administration of iron to an anemic patient who is obviously not responding to oral or intravenous iron therapy may be harmful.

Thus, from the data given above, it is possible to postulate that some patients with varied anemias will continue to absorb iron from the gastrointestinal tract as long as they are anemic, whether or not the body is in need of or can make use of such iron. Because the patient cannot excrete it, this iron is deposited in the liver, spleen, and other organs producing hemosiderosis and, if the patient lives long enough, probably hemochromatosis. Futile oral iron therapy in such a patient may actually be harmful by increasing the amount of iron absorbed. Transfusions probably only hasten the entire process. Whether the autopsy picture will be one of simple hemosiderosis or hemochromatosis (with cirrhosis) will depend upon the duration of the disease, number of transfusions and amount of iron intake.
1. Secondary hemochromatosis has been sharply separated from simple hemosiderosis by defining the former as "a condition acquired as a consequence of anemia, blood transfusions, or both, and characterized by increased hepatic and total body iron content and unequivocal portal cirrhosis of the liver."

2. Previously reported cases are critically reviewed in the light of this definition.

3. Two new cases of secondary (exogenous) hemochromatosis are reported.

4. Anemia is postulated as the basic etiologic factor in secondary hemochromatosis by causing increased iron absorption; iron introduced in the form of blood transfusions probably only accelerates a process already in progress.

5. Prolonged futile oral iron therapy may be harmful.

6. A plea is made for a strict concept of secondary hemochromatosis as well as for thorough documentation of future reports.

REFERENCES


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