EXOGENOUS HEMOCROMATOSIS RESULTING FROM BLOOD TRANSFUSIONS

By SIEVEN O. SCHWARTZ, M.D., AND SUNOLL A. BLUMENTHAL, M.D.

HEMOCROMATOSIS was first described by Hartman and Chausser in 1882 as "bronze diabetes" because of the association of skin pigmentation with diabetes mellitus. Von Recklinghausen in 1889 showed that the pigmentation of the skin and viscera was due to deposits of hemosiderin and hemofuscin. Hemochromatosis was considered quite rare, being clinically diagnosed only three times in 160,000 admissions to the Johns Hopkins Hospital, and on postmortem examination only four times in 5,000 autopsied cases at the Bellevue Hospital. There were less than 100 cases in the literature before 1920. By 1935, Sheldon43 was able to collect 311 acceptable cases and at the time of the last complete review of the literature in 1941 there were 436, indicating either a growing incidence or, more likely, a keener awareness and consequently more frequent recognition of the disease.

Classically, hemochromatosis occurs in the male, the ratio being 2.95 males to 16 females in Sheldon's series. It is practically unknown before the age of 20 and has its peak incidence between 45 and 55 years. The fully developed disease presents: (a) an enlarged liver (caused by a hypertrophic cirrhosis); (b) a bronze pigmentation of the skin, which usually has a peculiar slaty blue or metallic appearance;27 (c) diabetes mellitus of a severe type; and (d) a form of sexual hypoplasia characterized by impotence and an alteration of the hair distribution.27 However, one or more of these features may be absent.21 Pathologic characteristics are: (i) the pigment deposition; (ii) the fibrotic changes; (iii) the cellular degeneration in certain of the parenchymatous organs, this being the least prominent. The disease is inevitably fatal, death resulting either from the diabetes or from cirrhosis of the liver. The life expectancy in Butt and Wilder's6 series varied from one month to 13 years, averaging one and one-half years from the time the diagnosis was made. Sheldon puts the figure considerably higher, stating that the average terminal period is 18 ½ years.

Anemia is very rare in hemochromatosis, the average blood values being 4.1 million red cells and 80 per cent hemoglobin.

The two kinds of pigment found in hemochromatosis are hemosiderin and hemofuscin. Hemosiderin is an iron containing pigment, deep yellow in color, the particles varying in size from fine granules to larger masses which may be visible to
EXOGENOUS HEMOCROMATOSIS

the naked eye. Hemosiderin contains about 55 per cent iron. Its reactions are not
typical for ferric iron and there is no reaction for ferrous iron. Cook9 considers it to
be some form of colloidal ferric oxide physically combined with an organic sub-
strate. Hemosiderin is the predominating pigment of hemochromatosis and has an
extreme affinity for gland cells of both external and internal secretion. The greatest
amounts are found in the liver and pancreas, but there is no secreting gland in the
body that may not be affected. Striking exceptions to involvement are the kidneys
and the germinal epithelium of the testes. The former has only a moderate degree of
pigmentation, confined in most cases to the convoluted tubules of the second order,
while the latter usually escapes altogether. Striated muscle is, but smooth muscle
is not affected. In at least 90 per cent of the cases, the heart muscle is pigmented,
often by large amounts. Considerable quantities of pigment are found in the retic-
ulo-endothelial system. They occur in the Kupffer cells of the liver, the alveolar
endothelium of the lung, and in the spleen. In structures where there is much pig-
ment in the tissue cells, there is almost always pigmentation of the connective tissue
as well; this being especially so in the liver and pancreas.

Hemofuscin is a dark, almost black, pigment which contains no iron. It contains
about 3.7 per cent sulphur and is probably related to melanin. In hemochromatosis
it occurs to a slight extent in the epithelial cells of the glandular organs, but with
more frequency in the connective tissue, especially that of the spleen. There is
nearly always a large quantity in the heart muscle, but its site of election is the
smooth muscle of the genital and alimentary tracts, and the smooth muscle of
arteries.

An invariable feature of the disease is cirrhosis of the liver, usually of the hyper-
trophic type. The pancreas is also constantly affected, though usually less severely.
In contrast to the changes which occur in the liver, pigmentation and cirrhosis do
not always go hand in hand in other organs and there may be an advanced inter-
stitial pancreatitis with only a small amount of hemosiderin. The spleen nearly
always shows some fibrosis as do the heart, thyroid and salivary glands. The fibro-
sis, both in the liver and pancreas, has usually been considered the result of irritation
produced by the iron pigment. Sheldon, however, concluded that the two
processes, namely hemosiderosis and fibrosis, are independent of each other. Herbut
and Tamaki21 agree with this view and emphasize the fact that fibrosis occurs
almost exclusively in the liver, pancreas and spleen, and is not found in other organs
in spite of the fact that hemosiderosis may be very severe in them. They believe
that the excess of fibrous tissue in both pancreas and spleen is due to portal hyper-
tension. Degenerative changes in the parenchymatous cells do not occupy a promi-
nent place apart from the direct mechanical damage to the cells by the surrounding
fibrous tissue. Even where there is no pigment it is common to see collections of
degenerated cells surrounded by thick rings of fibrous tissue.

Chemical investigation reveals a great increase of iron in the various organs
which may be 50 to 100 times normal in the liver, pancreas and salivary glands.
The total amount of iron in the body has been estimated at from 20 to 58 grams, of
which as much as 38 grams has been found in the liver. Spectrographic studies have
revealed an increase of calcium in the tissues paralleling the increase in iron; ex-
ceptions being the lung, trachea and urinary bladder, which have less calcium than the control tissues, but have a marked increase of potassium. An increase of copper has been noted in most tissues, exceptions being the suprarenals and jejunum which have normal values, and the kidney which has less than normal.

**Relation of Hemochromatosis to Various Etiologic Factors**

Soper reported a typical case of hemochromatosis in a metal worker who was in contact with large amounts of copper, lead and zinc. Creed had a man who drank wine from a barrel lined with copper, while Gray described the case of a copper miner. Lawrence reported on the familial incidence of the disease in a family of nine siblings. Of the 4 males, 2 had typical hemochromatosis, a third had a borderline case, while the fourth was unaffected. Vitamin A deficiency with defective intestinal mucosa has also been postulated as possibly responsible.

Iron metabolism in hemochromatosis: Although studies made by Keilin in 1926 on the tissues of a case of hemochromatosis did not reveal any obvious disturbance in the intracellular metabolism of iron, it is felt that the iron cytochrome is undoubtedly subject to replacement in health as a result of the normal wear and tear of the tissues, and may be left in a form which the cells are unable to excrete when due for replacement. This would also account for the increased copper, since Elvehjem has shown that copper is necessary for the formation of cytochrome. In normal individuals, iron is taken in the diet in amounts of from 8 to 10 milligrams daily, partially absorbed in the duodenum, and excreted in minimal amounts through the large bowel and the kidneys. Iron is stored in the liver and only a slight trace is excreted in the bile. The body normally contains less than 5 grams of iron, more than half of which is in the hemoglobin. In hemochromatosis, the body excretes some iron in the stools, but none in the urine or bile. The iron accumulates in the body, as much as 58 grams having been reported.

The dietary intake of the average individual would provide enough iron for normal blood formation with an excess of from 25 to 50 grams by the age of 45 or 50 if the disease were congenital. If this were so, one might even expect to find cases with a familial incidence. Such have indeed been reported, but for some reason have attracted little attention.

Howard and Stevens, McClure, Fowler and Barer, and Dry have all shown that iron absorption is no greater in hemochromatosis than in normal patients. Fowler and Barer however, had an early case which did demonstrate increased absorption over a short period of study. Marble and Smith, in 1939, gave iron to a patient with hemochromatosis for a twelve day period. Absorption was 1.8 milligrams per day, the same as in a normal control. Sachs, Levine and Griffith showed the average normal whole blood iron to be 50 micrograms, and copper to be 0.132 micrograms per 100 cc. In their 3 cases of hemochromatosis the values for whole blood iron ran from 37 to 44 micrograms and copper from 0.130 to 0.156 micrograms. They thought that the low iron values were due either to the slight anemias which were found in all 3 cases or that the increase in the deposition of iron in the tissues tended to reduce the quantity of circulating iron.

**Experimental Hemochromatosis:** Muir and Dunn, in 1915, produced a rapid he-
molytic in rabbits by injecting an immune body intravenously. They demonstrated
that most of the iron resulting from destruction of the red cells was deposited in
the liver, spleen, and kidney on the fourth and fifth days. After the ninth day these
organs contained little over the normal amount of iron. Rous and Oliver, in 1918, injected rabbits with rabbit blood for several months without producing hemosiderosis. They did, however, demonstrate hemosiderin deposits in the liver. Mallory, in 1921, gave rabbits copper acetate for as long as eleven and a half months. He produced pigmentation, similar to hemofuscin, and cirrhosis in three rabbits. He believed that hemofuscin is changed to hemosiderin in some way and, after saturating the liver, is deposited in the pancreas, adrenal, thyroid, spleen, heart, skin and stomach. Polson, in 1929, gave rabbits dialyzed iron intravenously for three months and then sacrificed them one week to fourteen months later. He demonstrated that the iron moved from the lungs to the liver via the spleen. No evidence of cirrhosis or hemosiderosis was noted in the liver. Cappell, in 1930, gave colloidal iron to rabbits and showed that the iron was taken up by the reticulo-endothelial system, later entered into loose combination with plasma protein and passed into the liver, kidney and spleen; there was none in the pancreas. Taylor, Stiven and Reid, in 1931, induced hemochromatosis by depancreatizing a cat, and giving it a poorly balanced diet. This was the first recorded experimentally produced hemochromatosis. Polson later extended his original experiment and gave iron subcutaneously and intraperitoneally for periods ranging from one to four years. Hemosiderin was deposited in the tissues, but no cirrhosis or hemochromatosis were produced. Menkin in 1934 gave intravenous injections of ferric chloride to rabbits for a number of weeks and produced hemosiderosis, showing that hemosiderin is not solely a product in the degradation of the hemoglobin but may result from a release of iron in the body fluids. In 1946, Herbut, Watson, and Perkins showed that in 2 of their 30 rabbits with alloxan diabetes there was an associated cirrhosis of the liver, and to a lesser extent of the pancreas. Here, for the first time, two of the three important manifestations of hemochromatosis were noted, produced experimentally in animals by a single agent. The third manifestation, namely hemosiderosis, was produced by feeding reduced iron to the surviving diabetic rabbits.

Relationship of Hemochromatosis to Metabolic Diseases

In 1945, Gillman, Mandelstam and Gillman pointed out the relationship of hemochromatosis to nutritional disturbances in pellagrins. Their study was based upon histologic examination of 500 liver biopsies in South African natives. They emphasize in subsequent studies that the excess of iron in the liver cell in cytosiderosis (hemochromatosis) can arise in only a limited number of ways, namely: by the increased mobilization of iron from the red corpuscles and other bodily stores; by increased absorption and diminished excretion; and by abnormal utilization with normal absorption. Excessive destruction of the red blood cells has long been regarded as a potential cause of cytosiderosis of the liver. In pernicious anemia and the hemolytic anemias, there is hemosiderosis but no cirrhosis. In malaria,
Considering the rarity of hemochromatosis, the development of this disease in anemic patients who have had multiple transfusions appears to be more than simple coincidence. It is possible that the disturbed intracellular metabolism resulting from the anoxia due to the anemia may be contributory, making proper disposal of the iron pigment impossible. Thus, there would be an accumulation of hemosiderin, with eventual fibrosis added to the previously deranged cellular metabolism.

Theoretically, hemosiderosis should be producible in many ways and by any means which will increase the iron in the body over physiologic storage levels. This should be more readily accomplishable in the male whose iron excretion is much more limited than that of the female. Perhaps this is one of the explanations for the remarkable disparity between the incidence of hemochromatosis in the two sexes. The female has the opportunity, by pregnancies and menstruation, to lose quantities of blood which would tend to keep the accumulation of iron down to a point where, at least until the menopause, the hemosiderosis would be retarded. The age incidence of the disease, too, fits this concept, since to develop the full blown disease at the age of 50 (assuming the condition to be congenital) there would have to be an average daily excess positive iron balance of from only 1 to 2.5 milligrams.

Many more transfusions would have to be given, to administer enough iron to compare quantitatively with the amounts demonstrated in hemochromatosis, than the numbers either in our own cases or those previously reported, since a transfusion of 500 cc. of blood contains approximately only 2.5 milligrams of iron. A satisfactory explanation for the recovery of 45 grams of iron in the liver in Chesner's case, after having received a total of 6 liters of blood or 2.75 Gm. of iron, on the basis of retention of transfused iron is still difficult to answer. We must, therefore, search for other factors which might be operative. Poor nutrition has been incriminated both clinically and experimentally, but we have no evidence of this in the present series. The only common denominator of our and other reported cases is anemia, regardless of type, for which the transfusions were given. As has been mentioned before, it is not inconceivable that the anoxia due to the anemia plays a contributing role by disturbing the intracellular metabolism, and thereby making the cell more susceptible to the deposition of iron. Significant additional amounts of iron are made available to these patients by oral administration which is universally done in the attempt to combat the anemia.

That the cases under discussion differ from the classic "idiopathic" hemochromatosis is indisputable. It is, however, worthy of note that there are enough of the prime features in common to suggest that these cases represent intermediate or early forms which in time would probably show more and more of the classic feature of the disease, since the typical case differs only in degree and extensiveness. Whereas classic hemochromatosis is characterized by fibrosis of the liver, pigmentation of the skin, diabetes mellitus, and sexual hypoplasia, of the cases reviewed here only 2 had clinically demonstrable diabetes and only 5 had skin changes worthy of note. There was no significant sexual hypoplasia in any of the cases. However, in 9 of the 13 cases there was a significant enlargement of the liver, and in all 12 of the 13 cases in which either autopsy or liver biopsy were obtained a
### Table 1.—Cases of Exogenous Hemochromatosis

<table>
<thead>
<tr>
<th>Author and Date</th>
<th>No. of case</th>
<th>Sex and Age</th>
<th>Primary Diagnosis</th>
<th>Duration</th>
<th>Number of Transfusions</th>
<th>Initial Blood Count</th>
<th>Last Blood Count</th>
<th>Marrow Findings</th>
<th>Skin</th>
<th>Liver</th>
<th>Spleen</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. M. Kark 1937</td>
<td>1</td>
<td>Male</td>
<td>Aplastic Anemia</td>
<td>9 years</td>
<td>290 (plus)</td>
<td>Hgb. 50% RBC 2.50 WBC 3,500</td>
<td>Hgb. 50 to 70%</td>
<td>Many red cells present but normal hematopoietic tissue somewhat deficient. Eosinophils and round cells plentiful. Extreme replacement of marrow with fat.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. R. Bomford and C. P. Rhoads 1941</td>
<td>2</td>
<td>Male</td>
<td>Aplastic Anemia</td>
<td>16 months</td>
<td>15</td>
<td>Hgb. 30% RBC 1.40 WBC 1,150</td>
<td>RBC 1.00</td>
<td>Slightly hypocellular with isolated areas of active hemopoiesis. No megakaryocytes.</td>
<td></td>
<td></td>
<td></td>
<td>1,500 Gms. Not enlarged.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Male</td>
<td>Pseudo-Aplastic Anemia</td>
<td>12</td>
<td>RBC 1.50</td>
<td>RBC varied from 1.0 to 2.00 WBC 2,000 to 3,000.</td>
<td>Hypercellular. Reduced number of megakaryocytes.</td>
<td>Blackish brown pigmentation of hands and arms.</td>
<td></td>
<td></td>
<td></td>
<td>1,840 Gms. 130 Gms.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Male</td>
<td>No Diagnosis</td>
<td>8 years</td>
<td>55</td>
<td>Hgb. 26% RBC 1.30 WBC 3,850</td>
<td>Hgb. 30% RBC 1.40</td>
<td>A partly mature marrow with few megakaryocytes.</td>
<td>Brown pigmentation.</td>
<td>Not enlarged</td>
<td>Slightly enlarged.</td>
<td>Present</td>
</tr>
<tr>
<td>R. MacKay 1942</td>
<td>5</td>
<td>Male</td>
<td>Aplastic Anemia</td>
<td>3.5 years</td>
<td>39.8 liters</td>
<td>Hgb. 22% RBC 1.05 WBC 4,100</td>
<td>RBC varied between 1.10 to 2.70.</td>
<td>Increased in amount. Deep brown color. Increased granulocytes in all stages. Increased lymphocytes. Normal megakaryocytes. Only occasional nucleated red blood cell.</td>
<td></td>
<td></td>
<td></td>
<td>2,400 Gms. 450 Gms.</td>
</tr>
<tr>
<td>K. Zeltmacker and M. Bevans 1945</td>
<td>6</td>
<td>65 male</td>
<td>Pseudo-Aplastic Anemia</td>
<td>1 year</td>
<td>12.8 liters</td>
<td>Hgb. 36% RBC 1.40 WBC 4,900</td>
<td>Varied from RBC 1.13 to 2.50. Hgb. 34% to 54%. WBC 2,600 to 6,100.</td>
<td>Very cellular with RBC/WBC ratio 1:1. Marked shift to left in nucleated RBC and diminished numbers of mature granulocytes.</td>
<td>Gray-brown</td>
<td>3,050 Gms.</td>
<td>250 Gms.</td>
<td>Fasting blood sugar 110 and 190.</td>
</tr>
<tr>
<td>G. H. Humphreys and H. Southworth 1945</td>
<td>7</td>
<td>58 female</td>
<td>Aplastic Anemia</td>
<td>3 years</td>
<td>32</td>
<td>Hgb. 19% RBC 1.00 WBC 10,000</td>
<td>Hgb. 95% RBC 4.00</td>
<td>Mild hypoplasia of marrow but no abnormal cells.</td>
<td>Normal</td>
<td>6 cm. below costal margin</td>
<td>Not palpable</td>
<td>None</td>
</tr>
<tr>
<td>C. Chesner 1946</td>
<td>8</td>
<td>14 male</td>
<td>&quot;Banti's Disease&quot;</td>
<td>7½ months</td>
<td>6 liters</td>
<td>Hgb. 3.9 Gm. RBC 2.50 WBC 4,000</td>
<td>Hgb. 6 Gm. RBC 2.50 WBC 3,000</td>
<td>Hyperplasia of the erythroid elements.</td>
<td>Pale</td>
<td>2,350 Gms.</td>
<td>3 fingers down from costal margin</td>
<td></td>
</tr>
<tr>
<td>S. O. Schwartz and S. A. Blumenthal 1947</td>
<td>9</td>
<td>19 female M. P.</td>
<td>Congenital hypoplasia of kidneys with chronic glomerulonephritis.</td>
<td>9 months</td>
<td>21</td>
<td>Hgb. 44% RBC 2.24 WBC 6,500</td>
<td>Hgb. 50% RBC 3.01 WBC 6,000</td>
<td>Relatively acellular, made up mostly of granulocytic cells with right shift.</td>
<td>Scaly maculopapular eruption.</td>
<td>5 cm. below the costal margin. 1,665 Gms.</td>
<td>Not enlarged 165 Gms.</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>73 female R. H.</td>
<td>Aplastic Anemia</td>
<td>2 years</td>
<td>23</td>
<td>Hgb. 50% RBC 1.72 WBC 9,000</td>
<td>Hgb. 19% RBC 1.12 WBC 6,900</td>
<td>Hypoplastic marrow.</td>
<td>Pale</td>
<td>900 Gms.</td>
<td>50 Gms.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>49 female C. K.</td>
<td>Anemia with hepatosplenomegaly</td>
<td>2 years</td>
<td>58</td>
<td>Hgb. 36% RBC 2.50</td>
<td>Hgb. 9% RBC 1.30 WBC 14,100</td>
<td>Hyperplastic marrow with moderate replacement by large primitive cells which may represent erythroid elements.</td>
<td>Dark color</td>
<td>1,980 Gms.</td>
<td>520 Gms.</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Author and Date</td>
<td>No. of case</td>
<td>Sex and Age</td>
<td>Primary Diagnosis</td>
<td>Duration</td>
<td>Number of Transfusions</td>
<td>Initial Blood Count</td>
<td>Last Blood Count</td>
<td>Marrow Findings</td>
<td>Skin</td>
<td>Liver</td>
<td>Spleen</td>
<td>Diabetes</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
<td>----------</td>
<td>------------------------</td>
<td>---------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>Female J. B.</td>
<td>Aplastic Anemia</td>
<td>9 months</td>
<td>65</td>
<td>Hgb. 45% RBC 2,34</td>
<td>Hgb. 22% RBC 1.99</td>
<td>Hypocellular marrow with small islands of normal erythropoiesis</td>
<td>Pale</td>
<td>Not enlarged</td>
<td>Not palpable</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>47</td>
<td>Female V. G.</td>
<td>Anemia with hepatosplenomegaly</td>
<td>4 years</td>
<td>75</td>
<td>Hgb. 12% RBC 0.70</td>
<td>WBC 9,300</td>
<td>Hypercellular marrow, Megakaryocytes normal, Remarkable increase in primitive red cells. No megaloblasts noted. Shift in granulopoiesis, with numerous giant band forms and metamyelocytes. Increased number of eosinophils.</td>
<td>Dark</td>
<td>8 cm. below the costal margin. 3,100 Gms.</td>
<td>4 cm. below the costal margin. 780 Gms.</td>
<td>None</td>
</tr>
</tbody>
</table>

**CASE 1. Autopsy: Autopsy refused. Skin biopsy:** Brown, iron containing pigment in secretory cells of the sweat glands, lesser amount in the sebaceous glands and diffuse distribution in the connective tissue and basement membrane. **Remarks:** Patient began to develop the peculiar skin changes of hemochromatosis and enlarged liver about 8 years after the beginning of the transfusion series.

**CASE 2. Autopsy:** Hemosiderosis and fibrosis of liver, pancreas and lymph nodes. Immature hypoplastic marrow. Liver firm, golden brown cut surface, pancreas deep brown.

**CASE 3. Autopsy:** Broncho-pneumonia of right lower lobe. Spleen brownish purple cut surface, liver abundant golden brown pigment around portal areas. Pancreas deep brown in color. Considerable hemosiderosis and multilobar fibrosis of liver and pancreas. Extramedullary hemopoiesis in spleen. **Remarks:** Prior to transfusions patient was treated unsuccessfully with iron, liver, copper and vitamins.

**CASE 4. Autopsy:** Typical findings of hemochromatosis with hemosiderosis and fibrosis of liver and pancreas. **Remarks:** History of severe nosebleeds from age of 5 to 7, bleeding tendencies and purpura with splenectomy at age of 13.

**CASE 5. Autopsy:** Liver brownish-red color; spleen brick red, Prussian blue reaction was positive in both organs. Periportal fibrosis and free iron demonstrated in reticulo-endothelial cells and parenchymal cells. Evidences of hemochromatosis noted in pancreas, lymph nodes and heart. **Remarks:** Previous history was negative.

**CASE 6. Autopsy:** Liver orange brown, loaded with hemosiderosis. Spleen had a small amount of iron pigment. Pancreas was heavily pigmented and fibrotic. Prostate, lymph nodes, adrenal, thyroid and heart contained pigment. Marrow showed evidence of regression toward a more immature state. Lungs emphysematous. Right heart enlargement.

**CASE 7. Autopsy:** Iron staining pigment in liver, pancreas, bone marrow thyroid, adrenals, spleen and lymph nodes. **Remarks:** This patient had a profound depression of erythrocyte formation for many years and had to be maintained on blood transfusions. Following removal of a mediastinal tumor her red count went back to normal and she remained well for one year when she developed an abscess in her thigh followed by acute ascites, jaundice and death.
Case 8. Autopsy: Hemosidero-fibrosis of the liver and pancreas and generalized hemosiderosis; portal cirrhosis of liver; recent thrombosis of portal and superior mesenteric veins with hemorrhagic infarction of the lower three fourths of small intestine; atelectasis of right lower lobe. Remarks: Patient had a splenectomy for "Banti's Disease." The spleen showed reticulum-cell hyperplasia with fibrosis. He was maintained by blood transfusions for seven months until his death.


Case 12. Autopsy: Post mortem liver puncture biopsy showed a diffuse hemochromatosis with cirrhosis. The periportal areas contained numerous histiocytes filled with dirty brown pigment similar to that found in the liver cells and Kupffer cells.

Case 13. Autopsy: Hemosiderosis and cirrhosis of liver. Hemosiderosis of pancreas and abdominal lymph nodes. Multiple accessory spleens. Acute edema of lungs, moderate ascites, moderate edema of both legs, fatty degeneration of myocardium. Terminal bronchopneumonia. Hyperplasia of the bone marrow. Remarks: Patient had a splenectomy because of a possible diagnosis of hypersplenism. A large spleen and several accessory spleens were removed. She went into shock just as the abdomen was being closed. Although the usual measures for anti-shock therapy were instituted she died a few days postoperative.
hemosiderosis and fibrosis of the liver were found. Of equal importance was the
finding of both hemosiderosis and fibrosis in all 11 cases where pancreatic tissue
was examined. In the thirteenth case, only a skin biopsy was obtained.

It seems important to recognize that in dealing with simple hemosiderosis, exog-
enous hemochromatosis with secondary fibrosis, and hemochromatosis of the idio-
pathic type we are dealing with varying gradations of the same aberration. From
observations made in our own cases, together with the findings of previous investi-
gators (both clinical and experimental), it may be concluded that the deposition of
excess amounts of iron will lead to irritation, fibrosis and ultimately to destruction.
Whether this is precisely the sequence of events that occurs in hemochromatosis is
unknown and seems to be somewhat controversial. It is not unlikely that other
factors besides the simple deposition of iron may be responsible for the fibrosis. We
are, of course, dealing here with a highly selected group of cases, all of whom had a
profound anemia which undoubtedly damaged the liver parenchyma as well as the
parenchyma of other organs, especially those with high metabolic needs. It is im-
portant in this connection to re-emphasize the fact that the organs most involved
in hemochromatosis are those with high metabolic levels and oxygen consumption.
The factor of hemolytic transfusion reactions, not by virtue of hemolysis but be-
cause of the accompanying fever and further parenchymatous tissue damage, may
well have been an aggravating circumstance. Although this was not of universal
occurrence its importance cannot be minimized.

One of the striking differences between the cases here reviewed and those of typi-
cal hemochromatosis is the marked difference in the ratio of males to females. In
endogenous hemochromatosis, the ratio is about 2.0 to 1 in favor of males. In the
present series, there are 7 males and 6 females, while in our own series all 5 were
females. Of further interest is the fact that, whereas the classic picture is practically
unknown before the age of 20, there were 3 cases in the present group between 14
and 21 years of age.

Fully developed hemochromatosis, showing all the manifestations of the disease,
will undoubtedly be encountered in time because of the increasing utilization of
blood transfusions and the greater longevity of patients having hematologic dys-
crasias. There seems to be a definite relationship between the degree of hemosidero-
sis and fibrosis and the factors of time and number of transfusions. By and large,
the patients receiving only relatively few transfusions or transfusions over a rela-
tively short period of time seem to show the least involvement, whereas patients
who receive many transfusions over long periods of time (cases 1, 4, 5, 11 and 13,
table 1) will have the greatest amount of involvement. It is obvious from the fore-
goin discussion that patients to whom blood is given for the purpose of replacing
lost blood will have no tendency to develop hemochromatosis since the iron is
simply being replaced as it is lost from the body.

Our own interpretation of endogenous hemochromatosis is that it is a metabolic
disease in which excess amounts of iron are absorbed from the gastrointestinal
tract. Whether this excess iron is absorbed due to the fact that there is a breakdown
of the barrier in the gut or whether there is an abnormally low serum iron, either
as a distinct abnormality or due to the avidity of various tissues for iron, we are
as yet unprepared to say. In those cases where iron is introduced into the body parenterally either in a free or combined state (as in the form of red cells which are eventually broken down to hemoglobin) and becomes stored, it is gradually laid down in the various storage depots because no mechanism of excretion exists. When the storage depots become overfilled, the parenchymatous cells, which under normal circumstances do not contain iron, will take up the excess. We believe that this same sequence of events occurs in endogenous hemochromatosis and hence the greater incidence in males and the reason for the occurrence of the disease in later life.

It is worthy of note that the underlying disease for which the transfusions are given is not of prime importance. Diagnoses included true aplastic anemia, pseudo-aplastic anemia, chronic uremia, and others. In this connection it is particularly noteworthy that there is never a significant anemia in the classic hemochromatosis.

Therefore, the assumption that these cases had hemochromatosis and were complicated by anemia, for which in turn the transfusions were given, is fallacious.

The therapeutic suggestion of venesections and iron deficient diet presents itself in the management of hemochromatosis. It is not thought that this regime will be curative, but may serve, by reducing the hemosiderin deposits, as an ameliorating factor in the course of the disease.

**Case Reports**

*Case 1. Marylin P.*

Patient was a 19 year old white female who entered the hospital with a history of weakness, dyspnea, headaches, anorexia, sore throat and sore tongue, generalized pruritic scaly dermatitis, and recurrent bouts of epistaxis for a year. Past history revealed that she had scarlet fever during childhood and frequent sore throats subsequently. During the year preceding admission she had been treated with iron for anemia. On examination she was found to be poorly developed, but well nourished. The skin was covered by a pale, tan, finely scaly, maculo-papular eruption involving the trunk and extremities. Blood pressure was 120/60. The temperature was normal. Transitory attacks of twitching and convulsions with mental aberrations were noted. Significant laboratory findings on admission were: Hgb., 44 per cent; RBC, 2.14; WBC, 6,500; polys, 82 (bands 1); eosinophils, 1; lymphocytes, 10; monocytes, 7. The red cells showed slight anisocytosis and poikilocytosis; the granulocytes, slight toxicity. Urinalysis: albuminuria +, with 15-20 WBC and occasional RBC per HPF. NPN, 304 mg. per 100 cc.; creatinine, 16.7 mg. per 100 cc.; total proteins, 7.2 Gm. per 100 cc.; serum calcium, 7.5 mg. per 100 cc.; inorganic phosphorus, 11.1 mg. per 100 cc. Marrow was relatively acellular and consisted mostly of granulocytes which showed a right shift. She was given Blaud's pills, multiple vitamins, intravenous fluids, and sodium and calcium therapy.

During the next several months she was in the hospital on three other occasions. During these, 18 transfusions of 500 cc. blood were given. The final admission was eight and one half months after the first because of an exacerbation of the uremic symptoms of weakness, nausea, anorexia, skin rash and epistaxes. The blood pressure had risen to 171/116. There were rales at both lung bases, an ascites, a palpable, tender liver 4 cm. below the costal margin, and ankle edema. The urine now had a plus albumin. Hgb., 50 per cent; RBC, 3.01; WBC, 6,000; polys, 85 (bands 13); eosinophils, 1; lymphocytes, 12; monocytes, 4. NPN, 161 mg. per 100 cc.; creatinine, 14.8 mg. per 100 cc.; calcium, 7.5 mg. per 100 cc. She gradually became more stuporous and died in uremic coma nine months after first entering the hospital. Three additional transfusions of blood were given during this admission.

On postmortem examination, bilateral hypoplastic kidneys were found. These showed a chronic recurrent glomerulonephritis which was chiefly intracapillary. There was also hypoplasia of the renal arteries and the aorta. In the liver (1,665 Gm.), there was marked hemosiderosis with reactive periportal
fibrosis and bile duct proliferation. The spleen (165 Gm.) showed a chronic reactive hyperplasia with hemosiderosis. There were also hemosiderosis of the lungs and lymph nodes and a slight interstitial pancreatitis. Other findings were the marked hypertrophy and dilatation of the heart, bilateral hydrothorax, ascites, anasarca, uremic pericarditis, beginning uremic colitis, and hemorrhagic infarct of the lower lobe of the right lung.

Fig. 1. Slight interstitial pancreatitis and increase in fibrous tissue. (H. and E. Stain) Case 1. 160 X

Fig. 2. Liver, showing slight increase in connective tissue (Mallory stain) Case 1. 160 X
Comment: This 19 year old girl had a severe anemia secondary to chronic uremia. During the nine month observation period, she received 21 transfusions of 500 cc. blood in addition to ferrotherapy. Her liver, lungs, lymph nodes and spleen showed hemosiderosis. The liver, however, already had some periportal fibrosis at the time of death. It is difficult to say whether the pancreatitis was part of the picture. There were no skin changes or diabetes in this case. It is of great interest that periportal fibrosis should be demonstrable as early as nine months after the start of transfusions. There is nothing in the underlying disease which in itself should have predisposed this patient to liver damage or fibrosis other than the anemia and the hemosiderosis.

Case 2. Rena H.

Patient was a 73 year old white female whose main complaints were weakness for five months, fatigue, and "pins and needles" sensations in the fingertips for four weeks. Some dyspnea on exertion, coldness of the feet, belching after meals, a dry tongue, and an 11 pound weight loss had also been noted. Past history was noncontributory. On examination she was found to be well developed and well nourished, pale, and with a yellowish tint of the skin. The tongue was coated. There was a loud, rough, systolic murmur heard at the apex, which was transmitted to the neck and axilla. The blood pressure was 135/70. There was some tenderness in the left upper quadrant. Liver was felt 1 centimeter below the costal margin. Large varicosities were noted in the lower extremities. There was an ankylosis of the left hand on an orthopedic basis. Significant laboratory data were: negative urines, stools and serologic findings. Gastric analysis after subcutaneous histamine: free acid, 29; total acid, 50. Normal BMR and EKG. NPN, 29 mg. per 100 cc.; blood sugar, 77 mg. per 100 cc.; cholesterol, 118 mg. per 100 cc.; cholesterol esters, 70 per cent. X-rays: Gallbladder showed good dye concentration and the roentgenologic examination of the gastrointestinal tract was negative. Blood count on admission was as follows: Hgb., 50 per cent; RBC, 3,100,000; WBC, 9,000; polys, 56; eosinophils, 2; lymphs, 34; monocytes, 8; anisocytosis, 2 plus; macrocytosis, 4 plus. Platelets, 110,000; fragility test, normal. Marrow: hypocellular, with marked diminution of both erythropoiesis and granulopoiesis and increase in lymphoid elements. She received liver extract and one blood transfusion without benefit during her four week hospital stay.

She was rehospitalized nine months later and on this admission it was learned that she had been taking phenobarbital every night for the preceding eight months, and on and off for the previous six years. Her symptoms were the same as before but her "arthritic" pains had increased and a rash had appeared over the back and shoulders. She was again extensively studied, received two transfusions and was sent home after four weeks. There were four other admissions, the last one twenty-three months after the first. This admission was because of a pneumonia and pyelonephritis. Five blood transfusions were given during this admission, but despite these and other supportive measures she progressively failed and died two and one half months later. She had received a total of 13 blood transfusions during the two years of observation.

On postmortem examination the following pertinent findings were noted: hypoplasia of bone marrow, hemochromatosis of liver, spleen and pancreas, icterus with purpura, left pyelonephritis with cortical abscesses, moderate coronary artery arteriosclerosis with myocardial fibrosis, healed endocarditis of tricuspid, mitral and aortic valves, old pleuritic adhesions (rt.) with "Durchwandrung" perihepatic adhesions.

Comment: This 73 year old patient was studied over a two year period, during which time she received 23 blood transfusions. Many of the transfusions were followed by severe febrile and hemolytic reactions, which, in retrospect, were probably due to the then unknown Rh factor. What aggravating role these reactions played it is impossible to say, but they may have produced enough liver damage to have at least contributed to the ultimate fibrosis of the liver and other organs. It is...
not thought significant that the blood was rapidly destroyed during these reactions rather than in the normal way. There is no evidence to indicate that the underlying aplastic anemia was in any direct way related to the hemochromatosis. This patient had no clinical evidence of diabetes or skin involvement.
It never became apparent what the cause of the marrow hypoplasia was. Phenobarbital and sulfa drugs were suspected but never incriminated.

Fig. 5. Increase of iron pigment in liver (Prussian Blue stain) Case 2. 320 X

Fig. 6. Periportal area with increase in connective tissue and infiltration with round cells. Hemosiderin pigment deposition is quite marked. (H. and E. stain) Case 2. 160 X

Case 2. Carrie K.

Patient was a 49 year old white female who entered the hospital with a history of weakness, palpitation, dyspnea, nervousness, anorexia and a 30 pound weight loss in the previous two years. During the
EXOGENOUS HEMOCHROMATOSIS

Four months before her present hospital admission she had received 11 transfusions for anemia at a private hospital. Except for a right sided oophorectomy in 1927, her previous history and family history were noncontributory. She took milk of magnesia quite frequently and occasionally aspirin for headaches. She was found to be well developed and well nourished. The skin was pale and had a slightly icteric hue.

There were a few small discrete submaxillary lymph nodes, a marble sized node in the left axilla, and a few palpable nodes in the inguinal region. The heart was enlarged to the left. A soft systolic murmur was heard at the apex and there was a systolic murmur at the base. The liver was moderately hard and could be felt 3 cm. below the costal margin. The spleen was felt 2 cm. below the costal margin.

Laboratory findings of interest were the following: Hgb., 36 per cent (5.6 Gm.); RBC, 2.50; WBC, 7,900; polys, 59; lymphs, 27; monocytes, 13; eosinophils, 1. Platelets, 170,000. Urines, blood serology and stools negative. Serum protein, 7.4 Gm.; inorganic phosphorus, 4.7 mg.; acid phosphatase, 0. Icterus index, 9. EKG: slightly abnormal, with left axis deviation. Sternal marrow revealed an extraordinary cellularity; the megakaryocytes were normal; granulopoiesis was intact; erythropoiesis was accelerated to a remarkable degree and showed a marked left shift with very primitive erythropoiesis predominating. X-rays of the bones and the gastrointestinal tract were negative. The chest x-ray showed a boot shaped heart and accentuated hilar markings bilaterally, but otherwise lung fields were normal.

She was given 6 blood transfusions during a period of eighteen days, and was discharged, significantly improved both clinically and hematologically. No satisfactory diagnosis was established.

She was readmitted six months later because of a recurrence of weakness. There were no significant changes in her physical findings. The blood findings now were: Hgb., 36 per cent (5.6 Gm.); RBC, 2.71; WBC, 10,400; polys, 49 (bands 37); myelocytes, 2; metamyelocytes, 10; eosinophils, 1; basophils, 1; irritation cell, 11; lymphocytes, 18; monocytes 18. This time she received 8 blood transfusions during a three week period.

Two months later she was admitted to another hospital. Her liver now was 9 cm. and the spleen 6 cm. below the costal margin. Hgb., 23 per cent (3.6 Gm.); RBC, 1.40; WBC, 6,300; polys, 63 (bands 45); lymphs, 9; monocytes, 6; basophils, 1; myelocytes, 10; metamyelocytes, 11. BMR was +40. Otherwise, nothing new was found. Despite a total of 20 blood transfusions during this four month hospitalization her blood count still remained quite low.

Thirteen months after her first hospitalization she entered still another hospital. Here she received 13 more blood transfusions and splenectomy was performed. Her postoperative course was stormy; she developed pleural effusions and an hemopericardium, and died about six weeks later. Most significant single contribution clinically during this hospitalization was the discovery of a mild diabetes.

Postmortem examination revealed a pigment cirrhosis of the liver; hemosiderosis of the liver, stomach, adrenal glands, and lymph nodes. There was an interstitial fibrosis of the pancreas with extraordinarily large amounts of hemosiderin deposits involving especially the islands of Langerhans. The marrow was hyperplastic and the extirpated spleen showed myeloid metaplasia. Other findings were a fatty degeneration of heart and kidneys; subacute fibrinous pericarditis; chronic abscess of left upper quadrant of the abdomen; left pleural effusion; and septicaemia (staphylococcus aureus).

Comment: This 49 year old woman was studied at four institutions during her two years of illness. Every conceivable diagnosis was made and all types of therapies used in hematology were tried without success. Even postmortem examination failed to explain the cause of her anemia, or cast light upon the type of maturation failure seen in the primitive erythrocytes.42

During the two years of study she received 58 transfusions of blood, most of them uneventfully. Of greatest interest in this patient was the recognition of early diabetes some time before her death, explained pathologically by the large amounts of hemosiderin deposits in the islands of Langerhans and by the fibrosis in the pancreas. She had extensive hemosiderin deposition in most organs and, significantly, cirrhosis of the liver. This patient's skin was quite dark, having become more so during her last few months. Unfortunately no skin biopsy was obtained—one of
the disadvantages of retrospective investigation. It may also be said in retrospect that the splenectomy was not justified since the enlargement of the spleen was apparently secondary (due to compensatory extramedullary hemopoiesis) rather than the cause of the anemia. (This case has been previously published.3)

Case 4. Jean B.

Patient was a 37 year old white female who entered the hospital because of malaise, fatigability, dyspnea, ankle edema and palpitation for one month. She was actively bleeding vaginally on admission and had just been discharged from another hospital where one blood transfusion was given. For twenty-three years she had had menorrhagia lasting from one to four weeks, associated with dysmenorrhea for which she frequently took 'Anacin' and 'Midol.' There had also been many nose bleeds during the last several months. The patient worked in a pie factory most of her adult life. She had had an appendectomy and had never been pregnant; denied having had syphilis or having received anti-leukic therapy. She was well developed and well nourished, and appeared pale and weak. The hair was dyed. The pupils were equal but asymmetrical and did not react to light or accommodation. There was a loud, blowing systolic murmur heard at the apex and base of the heart. Neither the liver nor the spleen were palpable. The extremities were covered by numerous large ecchymotic areas. A lemon-sized cystic mass was palpated in the left adnexa, and the uterus was in the cul-de-sac.

Only laboratory findings of significance were the negative serologic tests for syphilis, the hematologic findings, and the marrows. The blood revealed Hgb., 44 per cent (6.8 Gm.); RBC, 2,134; WBC, 3,150; polys, 65 (bands 13); lymphocytes, 27; monocytes, 8. Platelets, 7,000 (two days after blood transfusion).

Sternal marrow was replaced by fibrous tissue.

During the first three weeks in the hospital, 1,300 r units of Roentgen radiation were given to the area of the pelvis, following which the uterine bleeding stopped. She also received 8 blood transfusions which elevated her count to Hgb., 67 per cent (10.4 Gm.); RBC, 4,612; WBC, 5,050. For the next several months, her condition was fairly good except for an occasional transfusion reaction. In five months she had received 44 transfusions, in spite of which her count had been gradually dropping, being Hgb. 20 per cent, RBC 0.93, WBC 900 at this time. From this point her condition slowly deteriorated. Transfusion reac-
EXOGONOUS HEMOCROMATOSIS

...tions became quite frequent, even with washed red cells; epistaxes became troublesome and required packing; petechiae and ecchymoses became more numerous.

Eight and a half months after admission, following her sixty-fifth transfusion, she developed a thrombophlebitis of the left arm. In spite of the usual methods of therapy, the process continued to spread and the patient expired eight days later. Permission to perform an autopsy was refused. Post-mortem liver biopsy revealed a "hemosiderosis associated with increased fibrosis of the periportal tissues (very early cirrhosis)."

Comment: This 37 year old woman had an aplastic anemia of unknown etiology. She had taken "'Anacin' and "'Midol' intermittently for years but none of the usually incriminated drugs or agents had played an etiologic role. We speculated on the possibility that this case might have represented one of those rare instances, if indeed such conditions occur at all, in which true marrow "exhaustion" occurs from too protracted and severe a drain. Her menorrhagia dated back to the menarche 23 years previously. This is, of course, purely speculative, since we know nothing about the nature of the pelvic tumor or the blood findings at any time during the previous twenty-three years. Unfortunately, no postmortem examination was performed, but the liver biopsy showed unmistakable signs of early cirrhosis about nine months after the first transfusion. Actually, it cannot be assumed that this patient started depositing iron in the beginning since she was still bleeding and her transfusions served as replacement therapy. Thus, her early cirrhosis occurred in a period of less than eight months.

Case 5. Victoria G.

The patient, a Negro female, was 43 years old when she first entered the hospital because of weakness, dyspnea, orthopnea and "bronchitis" of one year's duration. For six weeks before admission she had noted vague chest pains, moderate epistaxes, blood streaked sputum, and paresthesias of the hands and feet. She had had "typhoid-malaria" during childhood, and anti-luetic therapy with arsenic and bismuth some years previously. She was well developed and well nourished, quite pale, moderately dyspneic, and coughed frequently. The heart was enlarged both to the right and left; loud systolic and presystolic murmurs were heard at the apex and the systolic murmur at the base was heard transmitted to the vessels of the neck. There was dullness at both bases, breath sounds were distant and rales were noted in the right base. The liver was felt 4 cm. below the costal margin and had a sharp tender border. The spleen was not palpable. External hemorrhoids were present. Moderate nonpitting edema of both ankles was noted. Fundoscopic examination revealed nothing remarkable.

Examination of urines, stools and serologic blood tests were noncontributory. The gastric contents contained 40° free and 60° total acid. NPN, 26 mg. per 100 cc; creatinine, 1.5 mg. per 100 cc; icterus index 7 units. Hgb., 12 per cent (1.8 Gm.); RBC, 9,300; polys, 71 (bands 15); eosinophils, 6; basophils, 1; lymphocytes, 11; hyperchromia 1 plus, anisocytosis, 3 plus. Tests for sickling were negative. The marrow was hypercellular; megakaryocytes were normal; primitive red cells dominated erythropoiesis, but there were no megaloblasts; granulopoiesis showed a slight left shift with numerous "giant band" forms and megalometamyeloctyes; eosinophils were extremely numerous. X-rays of the chest confirmed the cardiac enlargement, while those of the gastrointestinal tract were negative. The patient was given digitalis, diuretin, ammonium chloride, parenteral liver extract and 3 transfusions of 500 cc. of blood. She felt better and left the hospital in three weeks. No diagnosis was established.

During the next four and one quarter years she was treated at three different hospitals, receiving a total of 50 blood transfusions and a course of bismuth and arsenic. At the end of this time she was readmitted to the Cook County Hospital with symptoms essentially similar to the original ones. She appeared older than her chronologic age of 47 and was quite pale and dyspneic. The liver now was 10 cm. below the costal margin, and was firm and tender. The spleen was palpable on deep inspiration. Mild pitting edema of the ankles was present. At this time she had Hgb., 15 per cent (1.3 Gm.); RBC, 0.69;
cultures and blood and spinal fluid serology negative. In spite of 9 blood transfusions during an eighteen day period, supplemented by oral iron and parenteral liver therapy, her blood count remained at Hgb.
EXOGENOUS HEMOCHROMATOSIS

- 19 per cent; RBC, 0.93; WBC, 14,500; polys, 64 (bands 19); eosinophils, 13; lymphocytes, 21; monocytes, 1; metamyelocytes, 1. Marrow findings were unchanged.

At this time a splenic inhibition was considered as responsible for preventing the maturation of the erythrocytes and it was decided to perform a splenectomy. This was performed after a preliminary series of transfusions, elevating the blood count to Hgb., 58 per cent, RBC 3.68, WBC 6,300. In spite of the preparation and the administration of 1,000 cc. of blood during operation, the patient went into shock immediately after the removal of the spleen. She responded to antishock management and for the first few days postoperatively seemed to be in fair condition. However, she developed bronchopneumonia and died seven days after the operation. During this period, 3 more transfusions had been given. Her last blood count showed Hgb., 60 per cent; RBC, 3.76; WBC, 25,600; polys, 83 (bands 30); basophils, 1; lymphocytes, 15; monocytes, 1.

Pertinent postmortem findings were: Hemosiderosis and cirrhosis of the liver (3,160 Gm.), hemosiderosis of the pancreas and abdominal lymph nodes, hyperplasia of the marrow, multiple accessory spleens, terminal bronchopneumonia, fatty degeneration of the myocardium, and acute edema of the lungs. The extirpated spleen weighed 780 Gm. and showed a marked diffuse fibrosis. About thirty accessory spleens, measuring from 2 mm. to 4 cm., and weighing a total of about 80 Gm., were also removed at operation.

Comment: This 43 year old Negress had a profound anemia whose etiology, as that of case 3 which it most closely resembled, was never satisfactorily established. The anemia was characterized by a hypercellular erythroblastic marrow which showed evidences of a maturation arrest at a primitive stage and did not respond to any of the known anti-anemia preparations. Life was maintained by substitution therapy consisting of 75 blood transfusions during four and one-half years. This patient did not develop diabetes. Whether skin changes occurred is not known. The remarkable enlargement of the liver was on the basis of the marked hemosiderosis and fibrosis. Undoubtedly these changes made her a worse surgical risk and contributed to the fatal outcome of the splenectomy.

SUMMARY

1. Five patients who died as a result of a variety of diseases, all characterized by severe anemia for which numerous transfusions had been given, and all of whom developed features of hemochromatosis are presented.

2. Eight similar cases found in the literature are summarized.

3. It is postulated that the hemochromatosis developing in these patients is the end result of the deposition and subsequently irritating action of the excess amounts of iron in the parenchymatous tissues.

4. The underlying anemia and the not infrequent transfusion reactions are thought to act as predisposing factors for the development of exogenous hemochromatosis.

5. The name Exogenous Hemochromatosis is proposed for this syndrome.

6. The clinical similarities and dissimilarities and the differences in pathogenesis between exogenous and endogenous hemochromatosis are discussed.

REFERENCES


GORK, quoted by GILLMAN, MANDELSTAM, and GILLMAN.


HARTMAN AND CHAUSER, quoted by Sheldon.


KARK, R. M.: Two cases of aplastic anemia; one with secondary hemochromatosis following 290 transfusions in nine years, the other with secondary carcinoma of stomach. Guy's Hosp. Rep. 87: 343, 1937.

KRELIN, quoted by Sheldon.

KREMER, quoted by GILLMAN, MANDELSTAM, and GILLMAN.


EXOGENOUS HEMOCHROMATOSIS

28 ———: Failure of prolonged administration of iron to cause hemochromatosis. Brit. J. Exper. Path. 14:
73, 1913.
35 STASNEY, J.: Erythrophagocytosis and hemosiderosis in liver and spleen in sickle cell disease. Am. J.
Path. 19: 115, 1943.
36 TAYLOR, J., STIVEN, D., AND REID, E. W.: Hemochromatosis in depancreatized cat. J. Path. & Bact. 38:
793, 1931.
37 VON RECKLINGHAUSEN, quoted by Sheldon.
Int. Med. 73: 393, 1945.
EXOGENOUS HEMOCHROMATOSIS RESULTING FROM BLOOD TRANSFUSIONS

STEVEN O. SCHWARTZ and SUNOLL A. BLUMENTHAL