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CLINICO PATHOLOGIC STUDY OF
HEMOSIDEROSIS IN CHILDREN

ANNE W. IWAMASON
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NAME AND ADDRESS

DATE
A CLINICO-PATHOLOGIC STUDY OF HEMOSIDEROSIS
IN PORTAL CIRRHOSIS

Alan Williams Ames
B.A. Stanford University, 1956

A thesis submitted to the faculty of Yale University
School of Medicine in partial fulfillment of the re-
qurements for the degree of Doctor of Medicine.

Department of Internal Medicine
Yale University School of Medicine
1960
ACKNOWLEDGEMENT

This study is the fruit of the labors of five people. Without any one of them it could not have been accomplished.

Dr. William A. Tisdale provided the initial impetus for undertaking this study and posed the basic questions for consideration herein. Throughout its course he was constantly available for counsel; his assistance in the evaluation of the microscopic sections and in the final writing of the thesis was invaluable.

Mrs. Hazel Hubbell did the bulk of the actual physical labor involved. In addition to her regular full-time duties she good-naturedly spent many hours in the preparation of the five hundred microscopic sections that constituted the central core of the study.

Mrs. Suzanne Hart Barnett, also, graciously spent much after-work time in deciphering scribbling and typing the final manuscript.

In sharing the tedious burden of reviewing eighty hospital records, Miss Judith A. Taimi performed a great service. Of greater importance, however, was the moral support she provided, chiefly by virtue of her un-failing optimism and cheerful good spirits.

Sincere thanks are offered to these four friends by the fifth collaborator: the author.

A. W. A.
New Haven
May 23, 1960
INTRODUCTION

The earliest recognition in the medical literature of a syndrome characterized by cirrhosis, diabetes mellitus, and melanoderma was in a lecture on diabetes by Trousseau in 1865 (1). Von Recklinghausen in 1889 coined the name now most commonly used to designate this entity: hemochromatosis (2). More recently, Sheldon published in 1935 a monograph which provided a comprehensive review of the clinical, pathologic, and investigative experience with hemochromatosis. This work, by suggesting that the disease represented an inborn error of metabolism, gave impetus to the further study of possible genetic and metabolic pathogenic factors (3).

Despite the length of time that hemochromatosis has been recognized and studied, a theory generally accepted as explaining satisfactorily its etiology and pathogenesis has thus far not been evolved. As indicated by the context in which Trousseau first mentioned hemochromatosis, the earliest students of the disease considered it simply an interesting variant of diabetes (4). Many other etiologic possibilities were subsequently suggested, but most present-day theories have been derived from the concept of Sheldon that the primary abnormality is an inborn error of iron metabolism (3). According to workers following Sheldon, this metabolic error causes an enormously increased absorption of iron through the intestinal mucosa (5). These concepts have been included in two of the most recent theories, which differ, however, in the importance attributed to the ultimate accumulation of iron in the tissues. Finch and Finch consider the manifestations of hemochromatosis as results of the tissue damage produced directly by cellular iron loading (6). According to Dubin, however, the same metabolic error causes both increased iron
absorption and, independently, fibrosis of the liver and pancreas resulting in the clinical features of hemochromatosis (7).

The close association of portal cirrhosis with hemochromatosis has long been recognized (3). Some writers have considered portal cirrhosis the sole cause of hemochromatosis, which they regard as a variant of this type of cirrhosis, but most authors merely have mentioned the similarity of the histopathology in the two diseases and the high incidence of "harmless" tissue iron in typical portal cirrhosis (3,8,12).

The present retrospective clinico-pathologic study was proposed to investigate further the relationship of portal cirrhosis to hemochromatosis, hoping ultimately to understand better the nature of the latter's etiology and pathogenesis. Specific areas to be explored in reference to patients with portal cirrhosis were: (1) the incidence of stainable parenchymal and reticuloendothelial hepatic iron, (2) the relation of the degree of hepatic siderosis to hepatic structural and functional damage, (3) the correlation of the incidence of pancreatic with hepatic iron, (4) the relation of pancreatic iron to pancreatic fibrosis, and (5) the correlation of the incidence of splenic with hepatic iron.

MATERIALS AND METHODS

Case Selection and Pathologic Studies

All cases with a primary or subsidiary post-mortem diagnosis of "hepatic fibrosis" or "cirrhosis" at the Yale-New Haven Medical Center in the years 1952-1959 were selected from the files of the Department of Pathology. From the 130 cases thus obtained microscopic sections were made of formalin-fixed liver, pancreas, and spleen. Liver sections were
prepared with Masson's trichrome stain; sections from all three organs were stained for iron (hemosiderin) with the Hubbell modification of the Gomori technique, using 2% hydrochloric acid and 2% potassium ferrocyanide (9).

Liver sections from all cases were examined microscopically to substantiate the diagnosis of cirrhosis; 88 cases remained in this category and were separated into two major groups: 60 cases with typical portal (Laennec's) cirrhosis and 28 with other specific types (post-necrotic, cardiac, and biliary) or unclassified cirrhosis. Diffuse monolobular fibrosis, small isolated regenerative nodules (pseudolobules), active parenchymal degeneration in the form of alcoholic hyaline ("Mallory bodies"), and fatty hepatocellular changes, in the absence of congestive or bile duct alterations specific for cardiac or biliary cirrhosis, constituted the basis for the morphologic diagnosis of portal cirrhosis. In addition, a positive history of alcoholism was considered in evaluation of type of cirrhosis.

Semiquantitative grading of hepatic iron content was established with emphasis on hepatocellular rather than reticuloendothelial (Kupffer cell) iron. Cases without hepatocellular iron were divided into those with no stainable liver iron and those with only Kupffer cell iron; cases with hepatocellular iron were graded from 1+ to 4+, the amount of coincident Kupffer cell iron being disregarded. In the final tabulation of results, cases with 1+ and 2+ hepatocellular iron were grouped as "slight," those with 3+ and 4+ as "marked."

The extent of hepatic fibrosis was assessed by separating all cases into two groups: those with "moderate fibrosis" and those with "advanced fibrosis." Hepatocellular fat content was graded from 1+ to 4+. In the
final tabulation all cases having only a trace (1+) of fat were not included in the "significant fat" category. Marked involvement of hepatic parenchymal cells with clearcut alcoholic hyaline ("Mallory bodies") was noted. Also noted were liver sections containing typical "glycogen nuclei" (the nuclei appearing to contain single large empty vacuoles) (11).

Stromal and parenchymal pancreatic iron content was assessed in a manner similar to that for hepatic iron and ranged from trace (1+) to mild (2+), excepting one case with moderate iron staining in a non-portal cirrhotic patient. Siderosis was tabulated only as being "present" or "absent." The location of the iron, whether in fibrous, acinar or islet tissue, was noted but not included in the final tabulation.

Ferrocyanide-stained sections of pancreas could not be evaluated for fibrosis; instead, these data were obtained from the complete autopsy protocols.

The ferrocyanide-stained sections of spleen were evaluated for both the amount (from 1+ to 4+) and the location of iron. 1+ and 2+ iron were tabulated as "slight," 3+ and 4+ as "marked."

Clinical Studies

For the sixty patients with portal cirrhosis data regarding age, sex and race were available. However, hospital charts could be obtained for only 52 patients; the clinical data are based on the records of this group. Few charts were satisfactorily complete; many items in the history and physical examination were not mentioned and for some patients there were few laboratory data.

The 55 white patients were considered separately by sex and by age relative to the median age for their sex. The median age proved to be 57
years for men and 49 years for women. The five Negro patients were considered individually.

All but two of the patients who admitted to excessive alcoholic intake placed its duration at more than five years. The other two patients had drunk heavily for less than one year and were not included as chronic alcoholics. Dietary habits were poorly documented in the records; specific mention of several years' inadequate diet by the patient was a requisite for his inclusion in the "poor diet" category.

Patients with a history of either ankle edema (even those with known cardiac disease) or ascites were listed as having "fluid retention." Those with a history of hematemesis or melena were included in the category of "GI bleeding." Clearcut symptoms and signs of cardiac failure or a definite diagnosis of congestive heart failure was accepted for inclusion of a patient in this category. Conversely, only those patients with a well-established diagnosis of diabetes mellitus were considered as having the disease.

On the basis of physical examination patients were categorized as having "bronze pigmentation" whenever it was noted as present or doubtful. For inclusion of a patient in the group with "jaundice," however, his icterus had to be definite. "Hepatomegaly" included all those cases with livers felt to be 4 cm. (two fingerbreadths) or more enlarged. Ascites and edema, whatever the presumed cause, were considered as indicating "fluid retention." Patients were included in the "abnormal heart" grouping if they exhibited cardiomegaly, significant murmurs, or cardiac failure. Testicular atrophy, when described in the hospital record, was noted.

Admission hematocrits were available on almost all patients with hospital charts; values under 30% (9 gm.% hemoglobin) were considered as indi-
cating anemia. Serum iron determinations were available on only three patients and were so listed. Patients with elevated fasting blood sugars (more than 100 mg.%) or glycosuria (including a trace of glucose) during their hospital stay were carefully screened; those receiving intravenous infusions were not included in these tabulations.

Patients receiving transfusions were given from 1 to 53 pints of blood; they were listed simply as having been "transfused." Patients with the clinical picture of congestive heart failure at any time during their hospital course were so listed. Those patients with advanced liver disease, mental obtundation and asterixis were considered to have "hepatic coma." Finally, patients with hematemesis, massive rectal bleeding or melena (as demonstrated by the guaiac test) were considered together in the group "GI bleeding."

These detailed clinical features were not studied in the 28 cases of non-portal cirrhosis.

RESULTS

Table 1

The incidence of the various histologic characteristics studied in the liver, pancreas, and spleen in cases of portal cirrhosis are correlated with the extent of hepatic siderosis in Table 1. It is seen that 65% of the patients with portal cirrhosis exhibited stainable iron in the liver, 42% having hepatocellular iron and 23% having iron solely in the Kupffer cells. As stated before, many of the livers containing hepatocellular iron also contained Kupffer cell iron. However, in a given case, the amount of reticuloendothelial iron as compared to the amount of parenchymal
iron was typically slight; in many liver sections with mild to moderate hepatocellular siderosis no Kupffer cell iron could be found.

The extent of hepatic fibrosis apparently correlated with the extent of hepatocellular siderosis, the incidence of advanced fibrosis being 40% in cases without hepatocellular iron, 50% in those with slight hepatocellular iron, and 71% in cases with marked hepatocellular iron. In contrast, there was no relation between the incidence of Kupffer cell siderosis and the incidence of advanced fibrosis, the latter condition occurring in 36% of cases with only Kupffer cell iron and in 43% of those with no hepatic iron.

In evaluating the extent of hepatocellular fat, it seemed that the fat content varied inversely as the extent of fibrosis. This impression was strengthened by the low incidence (29%) of fat in cases with marked hepatocellular iron as compared to those without hepatocellular iron (70%). The significance of the high (83%) correlation of fat with slight hepatocellular siderosis is unclear. Fatty hepatocellular changes appeared about equally frequent in the livers with only Kupffer cell iron (64%) and in those without (76%).

No alcoholic hyaline was found in livers with hepatocellular iron. However, the incidence of these cytoplasmic changes was not significantly decreased in cases with only Kupffer cell iron (21%) as compared to those with no liver iron (24%).

The incidence of "glycogen nuclei" was greatly increased in the presence of hepatocellular siderosis. These nuclear changes occurred in 5% of cases with no hepatocellular iron, in 17% of those with slight and 43% of cases with marked hepatocellular iron.

There was a strong correlation between the presence of hepatocellular and pancreatic siderosis. In none of the 14 cases with only Kupffer cell
iron and in one of the 21 with no hepatic iron was pancreatic iron encountered. This was in contrast to the frequency of pancreatic siderosis in patients with slight (40%) and marked (67%) hepatocellular siderosis. The extent of pancreatic siderosis was never great, the amount of iron in the most severely affected pancreas corresponding roughly to 2+ (mild) hepatic involvement. The location of the iron was inconstant, the acinar tissue, however, being more affected than the fibrous tissue. Of especial interest, the islets were rarely and minimally involved.

The incidence of pancreatic fibrosis seemed not to be related to the extent of hepatocellular siderosis and was actually less in the patients with Kupffer cell iron (12%) than in those with no hepatic iron (64%).

Of the 21 cases with no hepatic iron, splenic siderosis was absent in 40%, slight in 50%, and marked in 10%. In the groups with only Kupffer cell iron and with slight hepatocellular iron, which were identical regarding frequency and extent of splenic siderosis, cases without splenic iron were much less frequent (7%). This lower incidence was associated with a greater incidence of slight splenic siderosis (78%); marked splenic siderosis remained uncommon (14%). The six cases of marked hepatocellular siderosis were associated with a striking increase in splenic iron. In one case there was no splenic iron; in two there was slight, and in three, marked splenic involvement with iron. In contrast to the situation in the pancreas, the location of the iron in the spleen showed great uniformity. In all cases the hemosiderin deposits were restricted to the red pulp—the white pulp (Malpighian corpuscles), blood vessels, and trabeculae being spared.

Table 2

The clinical and pathologic pancreatic abnormalities investigated are correlated with the occurrence of pancreatic iron in Table 2.
There was neither historical nor clinical evidence of diabetes mellitus in the 9 patients with pancreatic siderosis in contrast to the positive family histories and clinical indications of diabetes in several of the 31 patients without pancreatic siderosis. Pathologically, however, three (43%) of the seven cases of pancreatic siderosis for which post-mortem protocols were available were reported as having slight to marked pancreatic fibrosis. This contrasts with the lower incidence (24%) of pancreatic fibrosis in cases without siderosis. Of interest, the frequency of pancreatic siderosis had no effect on the frequency of hepatic "glycogen nuclei."

Table 3

Table 3 summarized the relation of many clinical aspects of portal cirrhosis and hemochromatosis to the incidence and extent of hepatic and pancreatic siderosis in 60 patients with portal cirrhosis.

This sample was comprised of 55 white and 5 Negro patients--32 men and 28 women. The median age in years for white men was 57; the mean was 58.6. For white women the median age was 49 years, the mean being 52.7. The difference in mean ages between the two sexes (5.9 years) did not prove to be statistically significant, although it is probable that if the older age for women in the general population were taken into consideration this difference of 5.9 years would attain statistical significance. The cases with little or no hepatocellular iron were fairly evenly distributed among the sex and age groups. Both male and old age predominance became evident, however, in the cases with marked hepatocellular siderosis.

The incidence of patients with a prolonged excessive alcoholic intake was uniformly high in all categories of hepatic iron deposition. The presence of parenchymal iron was associated with an incidence of poor diet (77%) higher than that for cases with no liver iron (50%) or with only
Kupffer cell iron (16%).

The frequency of a history of fluid retention correlated slightly with the incidence of iron in either parenchymal or reticuloendothelial cells. In cases with no hepatic iron the incidence of fluid retention was 50%; in those with only Kupffer cell iron, 67%; with slight hepatocellular iron, 69%; and with marked hepatocellular iron, 83%.

Jaundice on physical examination was noted more frequently in patients with parenchymal siderosis, being observed in 25% of cases with only Kupffer cell iron, in 50% of cases with no hepatic iron, and in 86% of cases with parenchymal iron.

Two of the three values for serum iron concentration which were available were on patients who were without hepatic or pancreatic siderosis. One determination was within the normal range (70 mcg.%) ; the other was elevated (140 mcg.%) but not in the range consistently seen in patients with idiopathic hemochromatosis (6). The third serum iron concentration was 130 mcg.-% and was determined in a patient with both slight hepatocellular and pancreatic siderosis.

There was no noteworthy correlation between variations in the incidence of the remaining clinical features (Table 3) and in the frequency and extent of hepatic and pancreatic siderosis. Such clinical features included: personal history of gastrointestinal bleeding, congestive heart failure, and diabetes; family history of hepatic disease, cardiac disease, and diabetes; evidence on physical examination of melanoderma, hepatomegaly, palpable spleen, fluid retention, testicular atrophy, and cardiac abnormality; laboratory data including low hematocrit, elevated fasting blood sugar, and glycosuria; and a course in the hospital including transfusion therapy, congestive heart failure, hepatic coma, and gastrointestinal bleeding.
In summary: in the sixty cases of portal cirrhosis the liver contained stainable iron in 65% of the cases; in 43% of the cases the parenchymal cells were involved. Pancreatic iron was found in 23% and splenic iron in 84% of the forty cases in which microscopic sections of these organs were available. Pathologically, the presence of hepatocellular iron was associated with an increased incidence (as compared to that in cases without hepatocellular iron) of hepatic "glycogen nuclei," pancreatic siderosis, and splenic siderosis; with an increased extent of hepatic fibrosis and splenic siderosis; and with a decreased incidence of hepatocellular fatty change and alcoholic hyaline. The presence of Kupffer cell iron was correlated with an altered incidence of only one pathologic parameter: splenic siderosis. Pancreatic siderosis was accompanied by an increased frequency of pancreatic fibrosis. Regarding clinical features, a correlation was apparent between the presence of marked hepatocellular siderosis and increased incidence of advanced age, male sex, histories of poor diet and fluid retention, and jaundice on physical examination.

By way of comparison, the 28 cases of non-portal cirrhosis encountered in this study are shown in Table 4. There were nine patients with post-necrotic cirrhosis, seven with cardiac cirrhosis, and three with biliary cirrhosis; nine additional cases could not be morphologically diagnosed with assurance and were labeled "unclassified."

The incidence of stainable hepatic iron in post-necrotic cirrhosis was comparable to that in portal cirrhosis in regard to both total hepatic (67%) and hepatocellular (44%) iron content. The cases of cardiac cirrhosis (all with histories of long-standing hepatic congestion), however, were remarkably free of hepatic siderosis; five of the seven cases exhibited no hepatic iron, and only one had hepatocellular iron. Two of the
three cases of biliary cirrhosis were without hepatic iron; in the third there was slight hepatocellular iron.

Of the twelve pancreases studied in the cases of classified non-portal cirrhosis, only three (one in each type of cirrhosis) were siderotic, all three appearing in cases with livers free of iron.

Eleven spleens in these same types of cirrhosis were examined. All four of the spleens containing marked amounts of iron were associated with Kupffer cell siderosis.
DISCUSSION

Three major aspects of hemochromatosis will be discussed: its definition, its pathogenesis, and its relationship to portal cirrhosis. Utilizing the observations made during this retrospective investigation, these general phases will be covered and the 5 more limited objectives of the study emphasized.

Definition or diagnostic criteria. At the time of the publication of Sheldon's monograph in 1935, the basis for the diagnosis of hemochromatosis was the clinical triad of cirrhosis, diabetes mellitus and bronze pigmentation (3). However, the frequent absence of one or more of these features in pathologically-established cases, and the occasional concurrence of all 3 in patients with simple cirrhosis pointed up the necessity for more exact pathologic and chemical diagnostic parameters. Many authors, most notably Finch and Finch (6), have stressed the demonstration of hepatic cirrhosis and hemosiderosis as being critical in definitive diagnosis. When confronted with these features in atypical cases, however, they have sought confirmation in laboratory determinations such as serum iron content, serum iron-binding protein saturation and bone marrow iron content. Similarly, Dubin (7) has advocated resolution of pathological uncertainty by the use of iron tolerance tests.

Purely morphologic features have formed the basis of diagnosis in the studies of Kleckner et al (12) and, more recently, MacDonald and Mallory (13). These latter investigators have formulated a rather rigid and restricting diagnostic tetrad, including: portal cirrhosis; siderosis of hepatic parenchymal, bile duct and stromal cells; pancreatic siderosis and fibrosis; and parenchymal siderosis in other organs. Neither clinical nor
functional factors were considered vital in the diagnosis by these authors.

These conflicts seem to indicate that no set of criteria, clinical, biochemical or morphologic, define adequately the disease or syndrome of hemosiderosis. The current study further emphasizes this diagnostic dilemma. Thus, over 40% of these patients with well-established Laennec's cirrhosis had abnormal liver cell iron content, many having hemosiderin in Kupffer cells and stomal tissue as well. Further, two-thirds of those with hepatocellular siderosis had pancreatic siderosis, many having pancreatic fibrosis and splenic hemosiderosis in addition. Morphologically, therefore, a spectrum of parenchymal iron-loading and tissue damage (as manifested by fibrosis) exists. On the one extreme is "pure" portal cirrhosis; on the other is "typical" hemochromatosis, with hepatic and pancreatic siderosis and fibrosis. Varying combinations of parenchymal and stomal changes exist between these two extremes, making any current set of criteria appear arbitrary and inadequate. The frequent occurrence of Kupffer cell and splenic hemosiderosis, even in cases without transfusion or iron therapy, seems to invalidate Dubin's concept (7) that reticuloendothelial siderosis separates "hemosiderosis" from "hemochromatosis." Similar observations have been well summarized by Bell (9). Occasional demonstration of hepatocellular iron and pancreatic changes in patients with non-portal cirrhosis (Table 4) further obscures the previously established morphologic classifications.

Pathogenesis. The morphologic points of departure for most theories of the pathogenesis of hemochromatosis have been the parenchymal siderosis and fibrosis of the liver and pancreas. Thus, various investigators have sought to relate the obvious over-retention of iron, the accumulation of hemosiderin in liver and pancreatic cells, and tissue damage as mani-
fested by cell loss and connective tissue over-growth.

Cell damage induced by "excessive" deposits of iron-containing substances has been regarded as the primary pathophysiologic phenomenon by many workers. Although not original with him, Sheldon (3) popularized this theory in his monograph, suggesting that the initial overload stemmed from an "internal error of metabolism." Indeed, later investigations have confirmed, in certain patients, the striking over-absorption of ingested iron across the intestinal mucosal barrier (14), thereby validating Sheldon's hypothesis. However, despite prolonged and massive iron feeding (14) and injection (13) in experimental animals, definite hepatic or pancreatic cell damage and fibrosis have not been demonstrated with certainty. Perhaps further refuting the iron-excess-cell damage etiologic concept is the finding here of no hepatic cell necrosis (Mallory bodies) in livers with heavy iron deposition. On the other hand, the coincidence of advanced hepatic fibrosis and siderosis and the less constant pancreatic siderosis and scarring might be interpreted as evidence that iron had, in the past, produced cell death and resultant fibrosis. Certainly, however, the major clinical manifestations of hepatic disease in these patients could be well-explained by the many parenchymal and sternal changes that were unaccompanied by significant siderosis.

Structural and functional changes of the liver itself have been considered by some as primary in the evolution of hemochromatosis. Early in this century, Simmonds (8) described hemochromatosis as simply a variant of portal cirrhosis, and others (15) postulated that hepatic fibrosis induced, in some undefined manner, abnormalities of iron metabolism. More recently, Rather (16) emphasized the possible sequence of liver damage - iron overload, indicating that intestinal iron absorption was often excessive in both Laennec's cirrhosis and idiopathic hemochromatosis. Ani-
mal experiments reported by Goldberg and Smith (17) have given strong support to this concept, leading them to postulate that hepatic injury (dietary, toxic or unknown) leads to both increased intestinal absorption and tissue binding of iron, with resultant hemosiderosis. In the current clinico-pathological survey, liver disease was (by definition) present throughout. Nonetheless, the impression was gained that various degrees of hepatocellular and pancreatic parenchymal siderosis were simply engrafted on the underlying cirrhotic process. In general, the most cirrhotic livers contained the most parenchymal iron, but actively-degenerating cells did not seem unusually vulnerable to iron deposition. Portal cirrhosis is known to be accompanied frequently by pancreatic fibrosis (18); hence, the pancreatic siderosis seen might well be secondary rather than primary. The deposition of hemosiderin in the liver, pancreas and spleen of many of the cirrhotic patients would, it seems, lend credence to the idea that hepatic disease, at least in some phases of activity, promotes abnormal intestinal absorption of iron and deposition of hemosiderin in tissue sites. These observations do not establish any definite relationship between the clinical and laboratory manifestations characteristic of hemochromatosis and morphologic alterations in the liver and pancreas.

**Portal Cirrhosis and Hemochromatosis.** Morphologically, aside from iron deposition, there is no constant feature which distinguishes the cirrhosis of unquestionable hemochromatosis from non-pigmentary portal (Laennec's) cirrhosis. Most observers have emphasized the rarity of alcoholic hyaline ("Mallory body") formation in hemochromatosis; this series, in which none of the cases of hepatic siderosis had alcoholic hyaline, tends to confirm this. MacDonald and Mallory (13) and Klechner et al (12), however, have described characteristic alcoholic hyaline necrosis in otherwise typical
hemochromatosis. Pancreatic fibrosis occurs frequently in uncomplicated portal cirrhosis (18) and can not be considered unique to hemochromatosis. In addition, as shown in this study, pancreatic siderosis may be present in simple portal cirrhosis. Thus, there is no clear morphologic separation between pigmented and non-pigmented portal cirrhosis.

Clinically, patients with portal cirrhosis and marked hepatic siderosis were set apart in several ways from those with portal cirrhosis alone. Histories of poor diet and fluid retention and physical evidence of jaundice were slightly more common in the former group. More striking, however, was the definite predominance of males (6/7) in the cases of marked hepatocellular siderosis. Thus, these cases seem a connecting link between portal cirrhosis, in which roughly equal numbers of males and females are affected (19,20), and hemochromatosis, in which about 90% of reported patients have been males (6,12). Otherwise, all the clinical manifestations considered characteristic of hemochromatosis (cirrhosis, diabetes, skin pigmentation, heart disease) are also present in uncomplicated portal cirrhosis (9).

SUMMARY

In a retrospective study of 60 post-mortem cases of portal cirrhosis abnormal parenchymal hepatic iron was present in 43%. Twenty-three percent of the cases studied had pancreatic siderosis, frequently associated with fibrosis, and 84% had splenic siderosis. Morphologically, hepatocellular iron was associated with striking hepatic fibrosis and pancreatic and splenic siderosis.

Only an increased incidence of elderly males and slight evidence of hepatocellular dysfunction (fluid retention and jaundice) clinically distinguished the cases with hepatic siderosis.

These observations suggest that the clinico-pathologic syndrome of
hemochromatosis blends imperceptibly with that of non-pigmentary portal cirrhosis. It seems that portal cirrhosis in some way predisposes to increased iron absorption and tissue deposition.
Table 1
Stainable Hepatic, Pancreatic, and Splenic Iron in Portal Cirrhosis

<table>
<thead>
<tr>
<th>Hepatocellular Iron</th>
<th>Number of Cases</th>
<th>advanced fibrosis</th>
<th>sig. fat</th>
<th>Mallory bodies</th>
<th>glycogen nuclei</th>
<th>sections available</th>
<th>iron</th>
<th>+</th>
<th>fibrosis *</th>
<th>sections available</th>
<th>iron</th>
<th>sl. marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>35</td>
<td>14</td>
<td>25</td>
<td>8</td>
<td>2</td>
<td>24</td>
<td>23</td>
<td>1</td>
<td>8</td>
<td>42</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>no liver iron</td>
<td>21</td>
<td>9</td>
<td>16</td>
<td>5</td>
<td>1</td>
<td>11</td>
<td>10</td>
<td>1</td>
<td>7</td>
<td>64</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Kupffer cells only</td>
<td>14</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>1</td>
<td>12</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Slight (1-2+)</td>
<td>18</td>
<td>9</td>
<td>15</td>
<td>0</td>
<td>3</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>31</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Marked (3-4+)</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>23</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>28</td>
<td>42</td>
<td>8</td>
<td>8</td>
<td>50</td>
<td>31</td>
<td>9</td>
<td>13</td>
<td>36</td>
<td>44</td>
<td>7</td>
</tr>
</tbody>
</table>

* %: Percentage of all patients for whom autopsy reports are available.
**: The 2 cases with pancreatic iron are included in this group.
Table 2
Clinical and Pathologic Pancreatic Abnormalities in Portal Cirrhosis

<table>
<thead>
<tr>
<th>Tissue Iron</th>
<th>Number of Cases</th>
<th>Historical</th>
<th>Clinical</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Personal hx. family hx. of diabetes</td>
<td>*</td>
<td>elev. fasting blood sugar</td>
</tr>
<tr>
<td>Absent</td>
<td>31</td>
<td>77%</td>
<td>0 4 15%</td>
<td>2 11% 3 21%</td>
</tr>
<tr>
<td>Present</td>
<td>9</td>
<td>23%</td>
<td>0 0 0%</td>
<td>0 0% 0 0%</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>100%</td>
<td>0 4 11%</td>
<td>2 8% 3 17%</td>
</tr>
</tbody>
</table>

*% = The percentage of all patients for whom the pertinent data are available.
### Table 1

*Possible Clinical Aspects of Hemochromatosis Correlated With Hepatic and Pancreatic Stainable Iron in Patients With Portal Cirrhosis*

<table>
<thead>
<tr>
<th>Tissue Iron</th>
<th>White Men</th>
<th>Black Men</th>
<th>White Women</th>
<th>Black Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hepatocellular iron</td>
<td>26*</td>
<td>15</td>
<td>11</td>
<td>10*</td>
</tr>
<tr>
<td>Slight hepatocellular iron (1-2+)</td>
<td>17*</td>
<td>5*</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Marked hepatocellular iron (3-4+)</td>
<td>5</td>
<td>1*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Kupffer cell iron only</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Without pancreatic iron</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>With pancreatic iron</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Liver disease</td>
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<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Family History</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>Physical Examination</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>Laboratory Data</td>
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<td>0</td>
</tr>
<tr>
<td>Hospital Course</td>
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<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*One additional chart available.*

**Note:**
- The denominator = number of men with available charts.
- The examination = number of women with available charts.

---

1. No additional chart available.
2. The examination = number of men with available charts.
3. Hct. < 30%.
Table 4

Stainable Hepatic, Pancreatic, and Splenic Iron in Non-portal Cirrhosis

<table>
<thead>
<tr>
<th>Type of Cirrhosis</th>
<th>Tissue Iron</th>
<th>No. of Cases</th>
<th>Adv. Fibrosis</th>
<th>Pancreatic Iron</th>
<th>Splenic Iron</th>
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<tr>
<td></td>
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<tr>
<td>Post-necrotic</td>
<td>no liver iron</td>
<td>3</td>
<td>3</td>
<td>+</td>
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<tr>
<td></td>
<td>Kupffer cells only</td>
<td>2</td>
<td>2</td>
<td>00</td>
<td>MM</td>
</tr>
<tr>
<td>slight hepatocellular</td>
<td>4</td>
<td>4</td>
<td>0000</td>
<td>OOS</td>
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<tr>
<td>marked hepatocellular</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no liver iron</td>
<td>5</td>
<td>1</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Kupffer cells only</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>marked hepatocellular</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>M*</td>
</tr>
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<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
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<td>Cardiac</td>
<td>no liver iron</td>
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<td>2</td>
<td>+</td>
<td>-</td>
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<td>Kupffer cells only</td>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>S</td>
<td></td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
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<td>2</td>
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<tr>
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<td>Kupffer cells only</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>M</td>
</tr>
<tr>
<td>slight hepatocellular</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>marked hepatocellular</td>
<td>3</td>
<td>1</td>
<td>++</td>
<td>OM</td>
<td></td>
</tr>
</tbody>
</table>

* This case also exhibited Kupffer cell iron
S = Slight
M = Marked
BIBLIOGRAPHY


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