A PATHOLOGICAL STUDY OF IDIOPATHIC HAEMOCHROMATOSIS AND ITS RELATIONSHIP TO SIDEROSIS IN LIVER CIRRHOSIS

by R. SINNIAH*

Institute of Pathology, The Queen’s University of Belfast, Northern Ireland

*Present address: Department of Pathology, University of Singapore.

HAEMOCHROMATOSIS refers to a general increase in body iron stores with tissue damage. The pathological criteria used for the diagnosis of haemochromatosis were those proposed by MacDonald and Mallory (1960). They were as follows: —

1. Cirrhosis of the liver of a “portal type”.
2. Excessive iron deposits in hepatic parenchymal cells, in connective tissue, and in bile duct epithelium.
3. Pancreatic fibrosis and haemosiderosis.
4. Parenchymal iron deposits in other organs of the body.

MacDonald (1964) expressed the view that haemochromatosis was related to portal cirrhosis and was not a specific disease entity. In 1965, MacDonald reviewed the incidence of haemochromatosis in different geographical areas and found the figures to be low in Ireland. As to the aetiology of idiopathic haemochromatosis it had been suggested by Biggs and Davis (1963) that haemochromatosis may be of pancreatic origin as oral pancreatin was supposed to depress iron absorption. The present study was therefore performed to determine the relationship of haemochromatosis to liver cirrhosis with siderosis, and also to study its incidence and presentation in Belfast, Northern Ireland. The role of the pancreas in hepatic siderosis was also reviewed.

MATERIALS AND METHODS

Three groups of cases of cirrhosis of the liver including idiopathic haemochromatosis were selected from autopsies performed at the Royal Victoria Hospital, Mater Infirmorum and City Hospitals, Belfast, from January 1, 1938 to December 31, 1966 inclusive. During this period 22,050 autopsies were performed. The clinical records were reviewed, and all histological material was re-examined. A control series of autopsies with extrahepatic disease were also studied with regard to the degree of liver siderosis and pancreatic fibrosis. The sections were stained with haematoxylin and eosin (H & E) and Perls’ reaction for haemosiderin. Liver cirrhosis was diagnosed according to the criteria postulated at the Fifth Pan-American Congress of Gastro-enterology in Cuba (Pan-American Congress of Gastroenterology 1956). The features described by Baggenstoss and Stauffer (1952) were used to diagnose micronodular cirrhosis of the portal type. Macronodular cirrhosis with the postnecrotic pattern was diagnosed with the criteria postulated by Baggenstoss and Stauffer (1952); and Steiner (1960). Cases were accepted as idiopathic haemochromatosis using the criteria postulated by MacDonald and Mallory (1960). Those cases were excluded from the haemochromatosis group.
in which there was a history of blood transfusions or of oral or parenteral iron administration at any time prior to the final admission to hospital.

**INCIDENCE OF LIVER CIRRHOSIS**

The frequency with which liver cirrhosis is found at autopsy varies from series to series. These figures probably depend on available hospital facilities, the frequency of autopsy and whether there is a particular interest in liver diseases. In the present study, there were 640 cases of liver cirrhosis, of which 170 were micronodular cirrhosis, and 40 cases that were not classified. Thus the incidence of liver cirrhosis was found to be 2.9 per cent of all autopsies performed during 1938 to 1966 inclusive. The incidence of idiopathic haemochromatosis was 68 per 100,000 autopsies. The incidence, sex distribution and ages are shown in Table I.

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**TABLE I**

*Incidence, sex distribution and ages in haemochromatosis in 22,050 autopsies*

| No. of cases | 15 |
|--------------|----|
| Incidence relative to 100,000 autopsies | 68 |
| Distribution Male : Female | 4 : 1 (12 : 3) |
| Average age (in yrs.) | 56 |
| range (in yrs.) | 20–80 – Female |
| | 28–70 – Male |

**CLINICAL DATA IN CASES OF IDIOPATHIC HAEMOCHROMATOSIS**

The clinical notes of cases with idiopathic haemochromatosis were consulted and some observations may be noted.

Syphilis or a positive Wassermann test had not been noted in any of the cases with haemochromatosis. Syphilis was recorded in 1.2 per cent of the autopsies performed in this Institute. A statement concerning excess intake of alcohol was made in the clinical records of 13.3 per cent (two cases) with haemochromatosis. The alcohol consumed was mainly beer or whisky.

Diabetes mellitus occurred in 53.3 per cent with haemochromatosis. Only 2.6 per cent of the patients autopsied in this Institute had a clinical diagnosis of diabetes mellitus. In Sheldon's (1935) review, diabetes mellitus was found in 59.8 per cent of cases with haemochromatosis. Finch & Finch (1955) observed diabetes mellitus in 82 per cent of their cases, and MacDonald and Mallory (1960) reported that only 30 per cent of their 57 patients with haemochromatosis had diabetes mellitus.

Forty-six per cent of cases with idiopathic haemochromatosis were diagnosed before death to have liver cirrhosis. In patients with haemochromatosis at the Boston City Hospital, a clinical diagnosis of cirrhosis was made during the final admission in 50 per cent of cases. (MacDonald & Mallory 1960).
PATHOLOGICAL ASPECTS

Hepatic lesions in haemochromatosis

The average weight of the liver was 1,950 g; range 1,300 to 3,200 g. Approximately 86 per cent (13) of the livers weighed over 1,500 g. This was in keeping with other studies of the liver in haemochromatosis. MacDonald and Mallory (1960) found the average weight of the liver was 2,135 g, 60 per cent weighing more than 1,500 g. In the present study 80 per cent (12) of the cases showed the liver cirrhosis to be micronodular or "portal" in type, and 20 per cent macronodular or "postnecrotic" in appearance. The cirrhotic liver had a reddish-brown colour. There was minimal fatty change in 20 per cent (3) of the cases, but no liver showed moderate or severe fatty infiltration. Mild lymphocytic infiltration was observed in all cases. Bile duct proliferation was seen in all cases, but it was moderate in only 60 per cent of the cases. Excessive deposits of haemosiderin pigment were present in all cases. The pigment was present in the parenchymal cells, the interlobular fibrous tissue and the bile ducts. The iron deposits were heaviest in the periphery of the lobules. Iron was also present in the Kupffer cells in 80 per cent of the cases. Figs. 1 and 2 show the micronodular or "portal" and macronodular or "postnecrotic" types of cirrhosis in idiopathic haemochromatosis. A summary of the macroscopic and histological features and other relevant observations are shown in Tables II and III.

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TABLE II

Findings at autopsy in idiopathic haemochromatosis

| Observations                              | No. of cases | Per cent |
|-------------------------------------------|--------------|----------|
| Average weight of liver                   | 1950g        |          |
| Liver > 1500g                             | 13           | 86.0     |
| Average weight of spleen                  | 340g         |          |
| Spleen > 250g                             | 9            | 60.0     |
| Ascites                                   | 8            | 53.3     |
| Oesophageal varices                       | 5            | 33.3     |
| Rupture                                   | 3            | *(60.0)  |
| Peptic ulcer                              | 3            | 20.0     |
| Primary hepatic carcinoma                 |              | 33.3     |
| Total                                     | 5            |          |
| Type:                                     |              |          |
| Hepatocellular                            | 5(4R. lobe)  |          |
| Cholangiocarcinoma                        | 0            |          |
| Mixed                                     | 0            |          |
| Portal vein thrombosis                    |              |          |
| Total                                     | 3            | 20.0     |
| No. associated with liver CA.             | 3            | **(100.0)|

*Expressed as a percentage of the total number of oesophageal varices.
**Expressed as a percentage of the total number of cases with portal vein thrombosis.
**Fig. 1.** Microscopic appearance of liver in idiopathic haemochromatosis showing advanced "portal" or micronodular type of cirrhosis. Small nodules of hepatic parenchyma are enclosed by fibrous bands. Haemosiderin is present in the parenchymal cells, Kupffer cells, fibrous bands and bile ducts. (Perls' stain x 110).

**Fig. 2.** Microscopic appearance of liver in idiopathic haemochromatosis, showing "postnecrotic" or macronodular type of cirrhosis. Broad bands of fibrous tissue enclose more than 2 to 3 lobules of liver cells. There are dark masses of iron pigment in the hepatic parenchymal cells and in the connective fibrous tissue. (Perls' stain x 110).
TABLE III

Histological features in the liver in idiopathic haemochromatosis

| Observations                        | No. of cases (15) |
|-------------------------------------|-------------------|
| Morphological appearances           | 80 per cent "Micronodular" type |
|                                     | 20 per cent "Macronodular" type |
| Regenerative nodules                | 80 per cent "Micronodular" type |
|                                     | 20 per cent "Macronodular" type |
| Infiltration with fat               | Mild 20 per cent |
| Internodular fibrous tissue         | 80 per cent narrow zones |
|                                     | 20 per cent wide zones |
| Bile ducts                          | Mild to moderate proliferation |
| Leukocytes                          | Mild – lymphocytes |

Evidence of portal hypertension

Splenomegaly (weight above 250 g) was present in 60 per cent of patients with haemochromatosis. Oesophageal varices were demonstrated in 33.3 per cent with haemochromatosis. Ascites was found in 53.3 per cent. Sixty per cent of the varices bled. MacDonald and Mallory (1960) demonstrated that approximately 30 per cent of haemochromatosis had oesophageal varices, and our findings are comparable (33.3 per cent). This is contrary to the findings of Sherlock (1963) who stated that oesophageal varices with haemorrhage were rare in haemochromatosis.

Peptic ulcer

Ulceration was found in 3.7 per cent of autopsies performed in this Institute. Peptic ulceration was observed in 20 per cent with haemochromatosis. MacDonald (1964) reported an incidence of 1.8 per cent peptic ulceration in idiopathic haemochromatosis, which was less than the incidence of 5.5 per cent in the same autopsy population. The increased incidence of peptic ulcer may be due to the more frequent alcohol intake in these cases causing gastric irritation and faulty nutrition. It has been suggested that in liver cirrhosis there is an increased level of circulating plasma histamine, due to decreased breakdown by the liver cells, and it is this increased circulating level of histamine which causes peptic ulcer by increasing gastric acidity; but the exact mechanism is still obscure.

Primary hepatic carcinoma

This was observed in 33.3 per cent of the patients with idiopathic haemochromatosis. Hepatocellular carcinoma was the most common type (91 per cent), and cholangiocarcinoma was found in 5 per cent. The right lobe of the liver was the commonest site for the development of the tumour. In MacDonald and Mallory’s (1960) series of 57 cases of haemochromatosis, 12 per cent had primary carcinoma of the liver. Reports of the incidence of primary hepatic carcinoma in idiopathic haemochromatosis have varied in the literature from 5.8 per cent (Sheldon, 1935) to 30 per cent (Willis, 1941), but the majority of reports indicate an incidence
of about 14 per cent. No haemosiderin pigment was detected in the hepatic carcinoma of patients with haemochromatosis.

*Portal vein thrombosis*

Clot in the portal vein was found in 20 per cent of livers in patients with haemochromatosis. All these patients had primary hepatic carcinoma of the liver. This increased incidence of portal vein thrombosis was related to the high incidence of liver cell carcinoma.

*The pancreas*

A summary of the findings in the pancreas in control and haemochromatosis patients are shown in Table IV. Twenty per cent of autopsies with extrahepatic disease showed interacinar and inter-lobular pancreatic fibrosis, with minimal lymphocytic or adipose infiltration. Loss of cells in the islets was seen in 7 per cent, and hyalinization in 2 per cent of the control autopsies. No diabetes mellitus was recorded in these cases.

| Types of cases | Controls (100 cases) | Haemochromatosis (15 cases) |
|----------------|----------------------|-----------------------------|
|                | No. of cases | Per cent | No. of cases | Per cent |
| Pancreatic fibrosis | 20 | 20 | 14 | 93.0 |
| Leukocytic infiltration | 1 | 1 | 1 | 6.5 |
| Islets of Langerhans | | | | |
| Total involved | 9 | 9 | 9 | 60.0 |
| Hyalinized | 2 | 2 | 6 | |
| Decreased cellularity | 7 | 7 | 3 | |
| No. with clinical diabetes mellitus | 0 | *0.0 | 5 | *55.5 |

*Expressed as a percentage of the total number of islets involved.*

In idiopathic haemochromatosis, 93 per cent of the patients showed some degree of pancreatic fibrosis, which was mainly inter-acinar and inter-lobular. Stainable iron was present in all cases, deposited mainly in the acini and connective fibrous tissue. In 6 of the 15 patients, the islets of Langerhans were hyalinized and in 3 there was clinical diabetes mellitus. In three further cases, there was decreased cellularity of the islets, and two of these patients suffered from diabetes. Thus, of the nine patients with hyalinization or poor cellularity of the islets, five had clinical diabetes mellitus. Macroscopically, the pancreas was usually larger than normal and firm, with a brownish-red coloration due to deposition of iron.
Sheldon stated that pancreatic fibrosis was present in at least 90 per cent of cases of haemochromatosis, which is similar to the findings in the present study. MacDonald and Mallory (1960) found that among 57 patients with haemochromatosis at the Boston City Hospital, all the patients had some degree of pancreatic fibrosis with haemochromatosis. In the present study, no definite association between hyalinization and decreased cellularity of the islets of Langerhans and diabetes mellitus was found.

**Haemosiderin in various organs in haemochromatosis**

Haemosiderin was found in the liver, pancreas and lymph nodes in all 15 cases of idiopathic haemochromatosis. In the adrenal glands the iron was deposited mainly in the zona glomerulosa and haemosiderin was found in the thyroid gland and spleen in 60-65 per cent of cases. Iron was present in the gastric mucosa, skin and kidneys in 50 per cent, and in the heart, bone marrow and pituitary in approximately 40 per cent of the patients. It was found infrequently in the lung parenchyma. The frequency distribution of iron in the various organs is shown in Fig. 3.

![Fig. 3. The distribution of haemosiderin in various organs in idiopathic haemochromatosis.](image)

**Effect of hepatic cirrhosis on iron deposition in the liver and pancreas**

The incidence of siderosis in the liver and pancreas was assessed in a series of 100 routine autopsied patients with extrahepatic disease, 170 with micronodular cirrhosis, 159 with macronodular cirrhosis and 15 with idiopathic haemochromatosis. The degree of iron deposition was expressed as grades 0 – 4, grade 0 being
negative, and grades 1 to 4 representing increasing amounts of stainable iron (Scheuer, Williams and Muir, 1962). All the sections were examined and graded under light microscopy.

There was haemosiderin deposition in the livers of 30 per cent of the 329 patients with liver cirrhosis (micronodular and macronodular), whereas only 5 per cent of the 100 patients with “normal” livers showed haemosiderin (Table V). The difference in the incidence of hepatic haemosiderin between controls and patients with liver cirrhosis was statistically significant ($\chi^2$ test $P<0.005$). The haemosiderin deposits also appeared to be greater in amount in the patients with liver disease than in the patients with extrahepatic disease. Of the 329 cases of liver cirrhosis, 3.6 per cent (12) showed an excess of iron in the liver cells, internodular fibrous tissue and Kupffer cells, which was indistinguishable from the livers of patients with idiopathic haemochromatosis. In the 100 control patients, there was no haemosiderin in any of the sections of pancreas. Of the 329 patients with liver cirrhosis, 5.4 per cent (18) showed excess iron in the pancreas, present as granules in the acinar cells and connective tissue. Of these 18 patients, 10 had grade 1, and 8 had grade 2 iron in the parenchyma, while the patients with haemochromatosis showed grade 3 to 4 iron deposition (Table V). However, there was no significant difference in the incidence of pancreatic siderosis between the cases with liver cirrhosis and extrahepatic disease ($\chi^2$ test $0.10>P>0.05$). Of the 12 cases of liver cirrhosis with grade 3 to 4 hepatic siderosis, there was a history of blood transfusions, iron therapy and excess intake of alcohol in seven instances. But in the remaining five (40 per cent) cases of liver cirrhosis with grade 3 to 4 hepatic siderosis, no exogenous cause for the excess iron in the liver could be found.

Causes of death

Although many factors played a role in causing death in each patient, an attempt was made to estimate from the observations at autopsy the most important cause in each case. The chief causes of death are shown in Table VI. The most frequent causes of death were hepatic insufficiency associated with primary hepatic carcinoma and haemorrhage from bleeding oesophageal varices in 53.3 per cent of the patients. Two of the 15 patients with haemochromatosis died of hypertensive heart disease and myocardial infarction due to a thrombotic occlusion in atheromatous coronary arteries. No deaths due to cardiomyopathy were seen.

Discussion

The incidence of haemochromatosis was reported by Finch and Finch (1955) to be 1 in 7,000 hospital deaths. MacDonald and Mallory (1960) found a high incidence of 1 in 461 autopsies at Boston. MacDonald (1965) reviewed the incidence of haemochromatosis and cirrhosis in different geographical areas. He found that the average incidence in countries other than the United States of America was 180 per 100,000 autopsies, with a range varying from zero in some South American countries, Holland and Hungary, to a figure of 2,770 in France. In the United States of America the average incidence was 178 per 100,000 autopsies. He found that Scotland had one of the highest rates in Europe, with an average of 234 per 100,000 autopsies. MacSween and Jackson (1966) found the
## TABLE V

**Incidence of hepatic siderosis, pancreatic fibrosis and siderosis in the groups with extrahepatic disease and liver cirrhosis**

| Disease                        | Number | Liver iron grade | Percentage involved | Pancreatic fibrosis | Percentage involved | Pancreas iron grade | Percentage involved |
|--------------------------------|--------|------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Control                        | 100    | 5 0 0 0          | 5.0                 | 20                  | 20.0                | 0 0 0 0            | 0                   |
| Micronodular cirrhosis         | 170    | 30 11 4 2        | 27.4                | 94                  | 55.3                | 2 2 0 0            | 2.2                 |
| Macronodular cirrhosis         | 159    | 27 19 5 1        | 32.5                | 96                  | 60.3                | 8 6 0 0            | 8.7                 |

χ² test P < 0.005

| Haemochromatosis               | 15     | 0 0 0 15         | 100                 | 14                  | 93.0                | 0 4 8 3            | 100                 |

χ² test 0.10 > P > 0.05

## TABLE VI

**Most important causes of death in haemochromatosis**

| Causes of death               | Haemochromatosis (15 cases) | Per cent |
|-------------------------------|-----------------------------|----------|
| Hepatic insufficiency         | 5                           | 33.3     |
| Associated liver carcinoma    | 5                           | 33.3     |
| Haemorrhage – total           |                             |          |
| From varices                  | 3                           | 20.0     |
| From peptic ulcer             | 3                           |          |
| Cardiovascular diseases – total|                            |          |
| Myocardial Infarct            | 1                           |          |
| Hypertensive heart disease    | 1                           |          |
| Pulmonary infection            | 1                           | 6.6      |
| Abdominal catastrophes – perforations, strangulations | 2 | 13.3 |
| No cause determined            | 1                           |          |
| Non-hepatic malignant tumours | 1                           | 6.6      |
rate in Glasgow to be just over 200 per 100,000 autopsies. MacDonald (1965) found that Ireland and England with figures of 17 and 40 respectively per 100,000 autopsies were among the lower rates in Europe. However, in the present study the incidence of idiopathic haemochromatosis in Belfast, Northern Ireland, was found to be 68 per 100,000 autopsies. The incidence of haemochromatosis relative to the number of cases with portal cirrhosis and postnecrotic cirrhosis was 1 : 22. All our patients with haemochromatosis were manual labourers or in a low-income bracket, which is similar to the observations of MacDonald and Mallory (1960). The average age at death was observed to be 60 years by MacDonald and Mallory, 55 years by MacSween and Jackson and 56 years in the present study.

Finch and Finch (1955) observed idiopathic haemochromatosis about ten times as frequently in males as in females (90.4 to 9.6 per cent). Sheldon (1935) found that the male sex was twenty times as liable to the disease as the female sex (95 to 5 per cent). In the present study, 80 per cent of the cases occurred in the male. One explanation for this disparity may be the ability of the female to unload considerable amounts of iron through menstruation, pregnancy and lactation. The average woman during her life-time loses from 10 to 15 g of iron through menstruation alone (Finch and Finch 1955). Pregnancy and lactation may account for losses of body iron several times this amount.

Kleckner et al (1955) found that approximately 23 per cent of their 35 cases of idiopathic haemochromatosis were not diagnosed until an autopsy had been done. A clinical diagnosis of haemochromatosis was made during the final admission in 50 per cent of patients at the Boston City Hospital (MacDonald and Mallory 1960), and MacSween and Jackson (1966) found that more than 66 per cent of their 37 patients were not diagnosed clinically as having haemochromatosis. In the present study, 53.4 per cent of the patients were diagnosed as having haemochromatosis only at autopsy. The failure to diagnose more than half the patients with idiopathic haemochromatosis has been due to the absence of the classical presentation with the triad of liver disease, diabetes mellitus and pigmentation of the skin being found in 40 per cent of the cases in the present study. In patients with idiopathic haemochromatosis, diabetes mellitus was observed in 78 per cent of the patients by Sheldon (1935), in 82 per cent by Finch and Finch (1955), in 27 per cent by MacSween and Jackson (1966) and in 53.3 per cent in the present study. Skin pigmentation was observed in 83.8 per cent of the cases of haemochromatosis by Sheldon, 85 per cent of the patients by Finch and Finch, 55 per cent by MacSween and Jackson and in 53.3 per cent in the present study.

The average weight of the liver in the patients with haemochromatosis was 1950 g – about 500 g heavier than in control groups. Fat infiltration was seldom seen in the liver. The cirrhosis in 80 per cent of the liver was “portal” or micronodular and in 20 per cent “postnecrotic” or macronodular in type. Sheldon in his monograph on haemochromatosis stated that diabetic coma was the most common cause of death (50 per cent). He also found that cirrhosis of the liver caused death in 11 per cent, of which approximately half died from haematemesis and the remainder from hepatic failure. Carcinoma of the liver was responsible for 7 per cent of the deaths, but myocardial failure was not a major cause of death. However, Finch and Finch (1955), Kleckner et al (1955) and MacDonald
and Mallory (1960) found that the most frequent cause of death in haemochromatosis was congestive cardiac failure due to myocardial siderosis. Horns (1949) and Levin and Galum (1953) found that the most important cardiac manifestations were congestive cardiac failure and cardiac arrhythmias. However, in accordance with the findings in the present study, MacSween and Jackson (1966) observed that the commonest cause of death in haemochromatosis was hepatic failure – 33.3 per cent of patients with haemochromatosis died of liver failure. There was an associated primary liver cell carcinoma in many of these patients. A primary hepatocellular carcinoma was found in 33.3 per cent of our patients. Gastrointestinal bleeding from oesophageal varices caused the deaths of 20 per cent of the cases in the present study. This is at variance with Sherlock’s (1963) view that portal hypertension is inconspicuous and bleeding from varices rare in haemochromatosis.

Demonstrable haemosiderin pigment was observed in a large proportion of livers from patients with liver cirrhosis, both micronodular and macronodular types. In the control patients without hepatic disease, haemosiderin in the liver was significantly less frequent (5 per cent) and slight in quantity. Thirty per cent of the 329 patients with micronodular cirrhosis and macronodular cirrhosis had haemosiderin in the liver cells, but only 3.6 per cent of the livers contained iron to the same extent as in cases with haemochromatosis (grades 3 to 4). In approximately 60 per cent of these there was a history of multiple blood transfusions, excess alcohol and iron intake to explain the presence of hepatic haemosiderin. Pancreatic siderosis was found in 5.4 per cent of the 329 patients with liver cirrhosis, but the iron deposition was light (grades 1 to 2) and not as heavy as in haemochromatosis. There is some degree of overlap between siderosis in liver cirrhosis and haemochromatosis, but the deposition of iron in the pancreas in the former is not marked. The demonstration of haemosiderin in the hepatic parenchymal cells of patients with liver cirrhosis is in agreement with the observations of other workers (Herbut and Tamaki 1946; Gillman and Gillman 1947; Bell 1955; Dubin 1955; Finch and Finch (1955); Zimmerman et al. 1961).

Finch and Finch (1955) have stated that on biopsy differentiation of idiopathic haemochromatosis from Laennec’s cirrhosis with secondary haemosiderosis is difficult. Sheldon (1935) emphasized the similarity between portal cirrhosis with iron and haemochromatosis, but stated “it is true that portal cirrhosis contains more iron than normal, but if haemochromatosis were an extreme development of this process, one ought to find intermediate cases, whereas these appear to be conspicuously absent. The difference in degree is so profound and so sharp that it constitutes a difference in kind”. However, the present study showed that the transition from liver cirrhosis with iron to haemochromatosis is a gradual one without a sharp distinction, and differentiation clinically is based on arbitrary features such as the level of serum iron, degree of hepatic siderosis, the presence of diabetes mellitus and skin pigmentation.

MacDonald (1964) expressed the view that the excess iron in the liver and body tissues in idiopathic haemochromatosis was caused by the presence of iron in alcohol, especially wine, cooking utensils and medications or “tonics”. MacDonald found that among patients with haemochromatosis at the Boston City Hospital,
85 per cent gave a history of excessive intake of alcohol, while 70 per cent of cases with portal cirrhosis took alcoholic beverages in excess. Thus, he postulated that as portal cirrhosis was accepted to be related to alcohol, and as the frequency of alcohol intake was approximately the same as in haemochromatosis, the two conditions were similar. However, Sheldon (1935) suggested that idiopathic haemochromatosis was an inherited disorder of iron metabolism, and cited family aggregations of cases. Finch and Finch (1955) noted one father-son combination with the disease. Sherlock (1963) postulated that haemochromatosis was transmitted as a “dominant” with incomplete penetrance or expression. Williams et al (1962) suggested that the propositi would represent the homozygous affected, and the relative with raised serum iron and skin pigmentation the heterozygote state. Crosby (1966) defended the position that haemochromatosis is an hereditary disorder of iron metabolism in which several genetically determined faults can produce the pathological changes. Sinniah (1969a) observed raised serum iron levels in the relatives of patients with idiopathic haemochromatosis and there was a familial clustering of cases. Cooking utensils, iron medications or “tonics” and blood transfusions were not contributory causes in the development of haemochromatosis in the propositi studied. In the above study there was excess alcohol intake in 54 per cent of the patients, but the average amount of iron absorbed was approximately 2.61 g, which was much lower than the 20.405 g found in the organs in haemochromatosis (MacDonald 1964). The transition between liver cirrhosis with iron and haemochromatosis may be a gradual one, but the degree of haemosiderosis in the liver, pancreas and other organs is not as severe as in haemochromatosis. The definition and diagnosis of haemochromatosis are not anatomical, the disease being recognized by clinical as well as pathological criteria. Thus, cases of liver cirrhosis with siderosis should be classified as pigment cirrhosis, unless there is a strong genetic evidence for idiopathic haemochromatosis.

The relationship between hepatic parenchymal damage and haemosiderosis is not clear. Walker and Arvidsson (1950) suggested that the haemosiderosis in South African natives was related to the high iron and low phosphorus content of their diets. This view has been supported by MacDonald and Baumslag (1964). Gillman and Gillman (1947) have suggested that the hepatic siderosis of patients with nutritional liver disease may be due to impairment of hepatic enzyme systems involved in iron utilization or storage. Charlton et al. (1964) proposed that alcohol itself may stimulate the production of gastric juice and permit increased absorption of iron. Murray and Stein (1965) observed no increase in iron absorption in normal rats with alcohol supplement to their normal diets. Tuttle et al. (1959) and Tisdale (1961) put forward the hypothesis that the increased iron absorption was related to the presence of collateral channels, for patients with cirrhosis had been reported who had developed haemochromatosis after shunt operations. Williams et al. (1967) conducted iron absorption and hepatic siderosis studies on 76 patients with chronic liver disease, including 29 who had a surgical shunt performed 1 to 11 years earlier. The authors could not correlate increased iron absorption with collateral shunting. Callender and Malpas (1963), Davis and Biggs (1964) and Deller (1965) all suggested that increased iron absorption was a frequent finding in portal cirrhosis. Davis (1961) and Davis and Biggs (1965) suggested that oral pancreatin can depress the increased absorption of iron in liver disease. Biggs and Davis
(1963) even suggested that haemochromatosis may be of pancreatic origin. Van Goidsenhoven et al. (1963) demonstrated a high incidence of abnormal pancreatic function tests in cirrhosis of the liver. MacDonald and Mallory (1960) and Sinniah (1969b) observed marked pancreatic fibrosis in over 50 per cent of patients with cirrhosis of the liver. It has been stated (Davis 1961; Biggs and Davis 1963; Taylor et al. 1931; 1935) that it is the pancreatic deficiency which allows increased absorption of iron. However, Murray et al. (1964) and Sinniah et al. (1973) have not been able to confirm this observation experimentally. They found that in animals with ligation of the pancreatic duct or with pancreatectomy no evidence of liver damage was seen. Pancreatic enzymes in stated doses did not depress iron absorption in these animals with normal livers. Thus the relationship between liver cirrhosis, pancreatic dysfunction and increased iron absorption and storage has not been resolved.

**Summary**

During 1938 to 1966 inclusive, 22,050 autopsies were performed by the Institute of Pathology, Belfast. The incidence of liver cirrhosis (640 cases) found at autopsy was 2.9 per cent and the incidence of idiopathic haemochromatosis (15 cases) was 68 per 100,000 autopsies. Eighty per cent of the patients were males. A “portal” or micronodular type of liver cirrhosis was found in 80 per cent of the cases and the remaining 20 per cent had a “postnecrotic” or macronodular pattern.

Hepatic insufficiency and haemorrhage from oesophageal varices were the most common causes of death. The incidence of primary hepatic carcinoma was 33.3 per cent and portal vein thrombosis was commonly associated with the hepatic carcinoma. Peptic ulcer was found in 20 per cent of the patients and in 3.7 per cent with extrahepatic disease. Diabetes mellitus was observed in 53.3 per cent of the patients with haemochromatosis and in 2.6 per cent of cases with extrahepatic disease. Approximately 50 per cent of patients with haemochromatosis were not diagnosed until autopsy. Haemosiderin pigment was present in 30 per cent of the 329 patients with portal and postnecrotic cirrhosis, but only 3.6 per cent of the livers contained iron to the same extent as in patients with haemochromatosis. Of these 3.6 per cent patients, 60 per cent had a history of multiple blood transfusions, excess alcohol and iron intake to explain the presence of haemosiderin, but no obvious cause was found in the other patients. There was some degree of overlap between liver cirrhosis with siderosis and haemochromatosis, but the deposition of iron in other organs was not marked in the former. Patients with liver cirrhosis and siderosis should be classified as pigment cirrhosis, unless there is a strong genetic evidence for idiopathic haemochromatosis. The relationship between liver cirrhosis, pancreatic dysfunction and increased iron absorption and storage is not fully understood.

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