The African Journal of MEDICAL SCIENCES

Volume 3

1972

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Melbourne

Afr. J. med. Sci. (1972) **3**, 205–211.

Pathology of the Liver in Chronic Pancreatic Disease in Ugandan Africans

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(*Received* 31 *July* 1971)

Summary. A combination of severe hepatic fatty change and moderate or severe haemosiderosis is a significant feature of chronic pancreatic disease presenting with the malabsorption syndrome. Simple hepatic fibrosis and true cirrhosis do not appear to be associated with chronic pancreatic disease.

Résumé. Une association significative d'une hémosidérose et d'une dégénérescence graisseuse du foie lors d'une affection chronique du pancréas fut observé par l'auteur dans le cadre du syndrome de malabsorption. En revanche l'affection pancréatique chronique n'est pas associée avec une fibrose simple ou avec une véritable cirrhose du foie.

Chronic pancreatic disease, presenting with the malabsorption syndrome, diabetes mellitus and abdominal pain is frequently seen in Ugandan Africans (Shaper, 1960, 1964; Banwell *et al.*, 1967). The aetiology and pathology are discussed briefly by Banwell *et al.* who reviewed the clinical and laboratory investigations. The pathology and pathogenesis has recently been described in detail by Owor (1970).

The associated changes in the liver in these cases, and their relationship to the pancreatic changes, have been described by Stein *et al.* (1965) and these are also briefly considered in the paper by Banwell *et al.* (1967). The aim of this paper is to describe the liver changes in a series of cases coming to post-mortem and to try to relate the abnormalities either to the primary aetiological factors that cause chronic pancreatic disease or to the secondary effects produced by this disease.

MATERIALS AND METHODS

The livers from fifty-six patients with chronic pancreatic disease who came to post-mortem at the Mulago Hospital, Kampala, Uganda, were examined carefully and sections were taken for histological processing. In the same manner livers from 112 unselected post-mortems were examined. These formed a control group. The pancreases of this control

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group were also examined macroscopically and sections taken for histological assessment. Two controls of similar age and sex were compared to one of chronic pancreatic disease within ±5 years. After standard processing, liver sections were cut and stained by haemotoxylin and eosin. When appropriate, sections were also stained by Perls' method for free iron, by silver impregnation for reticulin and by van Giesen's method for collagen.

In assessing the histological changes in the cases and in the controls particular attention was paid to the following features: the general liver architecture; the degree of portal fibrosis in non-cirrhotic livers; the presence, extent and distribution of fatty change in hepatocytes; the presence of free iron, its location in liver cells and/or Kupffer cells and its lobular distribution; the presence of Mallory bodies in the hepatocytes; the degree and type of portal infiltration by inflammatory cells and the presence of cholestasis or other changes associated with extrahepatic biliary obstruction.

RESULTS

Macroscopic findings

Thirty-five (63%) of the fifty-six livers examined showed a yellow or orange-yellow colour typical of fatty change in the liver. Only five (14%) of these fatty livers were heavier than normal, the rest were lighter, the range of the controls being 1200–1700 g. Those with a curious orange or red-brown colour were found to have both fatty change and an increase in iron in the parenchymal cells. This macroscopic picture is almost pathogonomic of chronic pancreatic disease in Uganda. In the control group, macroscopic fatty change was present in only nine (8%) cases and none showed the peculiar colouration produced by fat and iron.

TABLE 1. Hepatic fatty change

	Control (112)		Chronic pancreatic disease (56)	
	No. of cases	%	No. of cases	%
No fatty change	87	78	21	37
Moderate fatty change	16	14	7	13
Severe fatty change	9	8	28	50

A macroscopic diagnosis of cirrhosis was made in eight patients one of whom had an associated hepatocellular carcinoma. One patient had hepatocellular carcinoma without cirrhosis. In the control series, cirrhosis was noted macroscopically in twelve patients and none of them had hepatocellular carcinoma. Increased fibrous tissue in the portal areas without cirrhosis was observed in six patients, one of these was associated with obstructive jaundice. In the controls there were four with macroscopic portal fibrosis and two of these had schistosomiasis. Two patients who had been jaundiced in life showed bile staining of their livers. These patients did not have tumours or stones in the biliary passages. Ten patients were macroscopically normal and in the control series eighty-four cases were normal.

Microscopic findings

The main histological findings in the cases and controls are shown in Tables 1 and 2 and Fig. 1.

Histologically hepatic fatty change and fibrosis were graded into moderate and severe degrees:

Moderate fatty change. All the lobules are involved and less than 50% of the cells in the lobule are affected. Focal fatty change involving a small group of cells is excluded.

Severe fatty change. More than 50% of the cells in the lobule are involved and fat cysts are present.

Moderate fibrosis. Stellate fibrosis round the portal tracts with minor extensions into the parenchyma.

Severe fibrosis. Marked portal fibrosis extending into the parenchyma but without loss of lobular architecture.

TABLE 2. Hepatic fibrosis

	Control (112)		Chronic pancreatic disease (56)	
	No. of cases	%	No. of cases	%
No fibrosis	65	58	29	52
Moderate fibrosis	28	25	14	25
Severe fibrosis	7	6	5	9
Cirrhosis	12	11	8	14

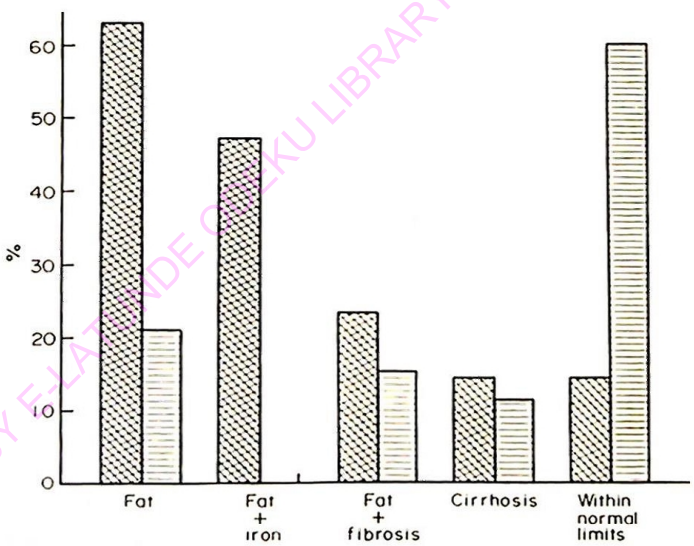

FIG. 1. Histopathology of the liver in chronic pancreatic disease (cross hatched columns) and controls (horizontally hatched columns).

Thirty-five (63%) of the cases had moderate to severe degree of fatty change and twenty-eight (50%) of the fifty-six livers had severe fatty change sometimes producing fat cysts. In the controls fatty change was seen in twenty-five (22%) of the cases and in only nine (8%) was the fatty change severe. This fatty change was more marked in the central parts of the

lobules but in many of them it was so marked that virtually every hepatocyte was affected. Twenty-one out of twenty-three cases with severe fatty change had clinically presented with features of malnutrition or malabsorption syndrome and four of these were known alcoholics.

A combination of fat and excess iron pigment in the same liver was a frequent finding. In twenty-six cases (47%) there was a considerable amount of stainable iron and in the majority of these the iron was mostly in the hepatocytes, particularly in the periphery of the lobules (Fig. 2). The sinusoidal lining cells and Kupffer cells contained very little iron. None of the controls had the combination of fat and iron. In two other cases, however, the pigment was seen only in sinusoidal cells and none in hepatocytes. These cases had no fibrosis or fatty change. A combination of fatty change and moderate or severe portal fibrosis was seen

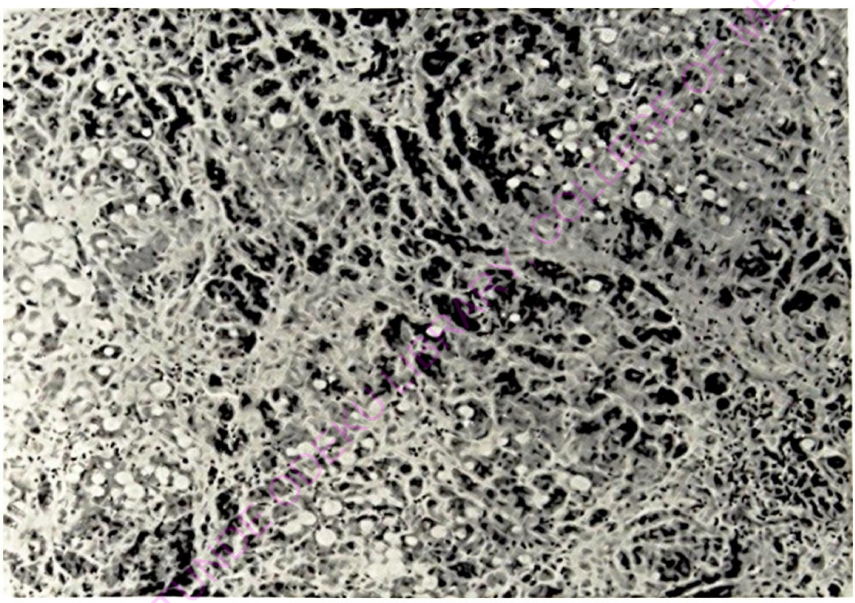

FIG. 2. Liver showing fatty change and haemosiderosis. Perls' reaction. ×160.

in thirteen cases (23%) and, in 15% of the controls but fibrosis without fatty change was seen in only one case of obstructive jaundice. Eighteen of the controls (16%) had fibrosis without fatty change. Chronic pancreatic disease was associated with cirrhosis of the liver in eight cases (14%) and six of these were fine cirrhosis some of which contained fat and iron pigment. Twelve of the controls (11%) had cirrhosis and three of these had fatty change as well but without iron. None of the controls was an alcoholic.

Chronic inflammatory cell infiltration around the portal tracts, in excess of normal limits was commonly seen (59%) but only eleven cases showed severe degree of inflammation. Lymphocytes formed the majority of these cells although some plasma cells were often seen. Acute inflammatory cells were rare and only one case of cirrhosis showed many polymorphs. Similar inflammatory changes were seen in the controls.

A moderate degree of cholestasis was seen in seven cases with gross fatty change although only one had clinical jaundice. There were four other cases with marked cholestasis due to obstruction of the common bile duct by fibrosis in the head of the pancreas.

Mallory bodies in hepatocyte cytoplasm are usually associated with alcoholism. They were present in small numbers in only one case, a non-alcoholic. Vacuolation of liver cells nuclei due to deposition to glycogen was seen in five diabetics.

DISCUSSION

The commonest abnormality in the liver in patients with chronic pancreatic disease is fatty change which was present in a severe degree in 50% of the cases in this series. This compares with a figure of 8% for the unselected group of post-mortems which served as a control. The accumulation of fat in the liver may be the result of direct injury to the liver cells or to a lack of the lipotrophic factors which are necessary for the normal metabolism of fat by the liver cell. The possible mechanisms involved in the development of hepatic fatty change have been discussed by Lombardi (1966). In chronic alcoholism where fatty changes are common in the liver (Leevy, 1962), the changes are probably due to a direct effect of the alcohol on liver cells and to some degree of malabsorption and malnutrition. As alcoholism has been associated with chronic pancreatic disease in some parts of the world it is necessary to consider whether the finding in Ugandan cases of chronic pancreatic disease merely reflect an alcoholic aetiology. In the great majority of cases there was no history of alcoholism and a few cases occurred in young people who would not have taken any alcohol. When the case histories were examined it became evident that nearly all the cases with gross fatty changes had evidence of malnutrition due to malabsorption, whereas over 60% of those who did not have fatty change had presented with diabetes with no evidence of malabsorption or malnutrition. The remainder were mostly individuals who were first discovered at post-mortem and who had no evidence of malabsorption. It seems probable therefore that the fatty change is secondary to the malnutrition caused by a failure of exocrine function of the pancreas, with lack of lipotrophic factors. Chronic pancreatic disease accounts for 65% of the cases who present with malabsorption in Uganda (Banwell *et al.*, 1967).

Several authors have referred to the relationship between chronic pancreatic disease and hepatic fibrosis or cirrhosis (Stinson, Baggenstoss & Morlock, 1952; Stein *et al.*, 1965), and they suggested that they had a common aetiology possibly related to childhood malnutrition. It must be stressed however that the aetiology of chronic pancreatic disease in Uganda is not known. It seems unlikely that either alcoholism or malnutrition accounts for the high incidence though it is possible that they may be co-factors. There is no definite evidence that the fatty changes characteristic of kwashiorkor progress to cirrhosis (Suckling & Campbell, 1957; Cook & Hutt, 1967). Stein *et al.* (1965) stated that pancreatic and hepatic fibrosis are more common among Ugandans than age–sex matched Americans. Conversely, they suggest that pancreatic fibrosis increases with hepatic fibrosis, suggesting that these are due to common factors. It is important however to distinguish in both organs the differences between a simple increase in fibrous tissue without parenchymal disorganization—hepatic fibrosis and pancreatic fibrosis—and cases with parenchymal disorganization—hepatic cirrhosis and chronic pancreatic disease (Owor, 1970). The increase in pancreatic fibrous tissue with age, for example, is a different process from fibrosis of chronic pancreatic disease.

In the present series there was some increase in hepatic fibrous tissue, extending from the portal areas, but with normal architecture in 31% of the 112 unselected post-mortems and in 34% of the fifty-six cases with chronic pancreatic disease. Similar increase in portal fibrous tissue was seen in 20% of sixty-two cases with normal pancreas and in 28% of fifty cases with simple pancreatic fibrosis. Conversely simple pancreatic fibrosis is found in 19% of forty cases with normal livers and in 26% of thirty-eight livers with simple fibrosis. This suggests that there is no association between simple fibrosis in the two organs. This is not surprising as the factors giving rise to hepatic fibrosis such as schistosomiasis of the liver and chronic intestinal disease would not be expected to affect the two organs. Hutt (1971) has observed that liver changes in the Ugandan Africans are usually a result of more than one condition. However, it is pointed out that cholelithiasis is not a likely cause of pancreatic or hepatic fibrosis in Ugandan Africans because cholelithiasis is rare in Africans (Owor, 1964). In this study none of the cases of chronic pancreatic disease or controls had cholelithiasis.

Microscopic evidence of true hepatic cirrhosis was found in 14% of the cases with chronic pancreatic disease and in 11% of the unselected adult post-mortem population. This suggests that the cirrhosis that occurs in cases of chronic pancreatic disease is a chance association rather than suggesting that they are aetiologically related.

Excess iron absorption is a recognized consequence of exocrine pancreatic malfunction (Andersen, 1938; Davis, 1961), although the exact mechanism is not well understood. In this study, excess iron was seen in twenty-eight cases (50%) and in twenty-six of these the iron was present mostly in the hepatocytes and little in the Kupffer cells. The two cases with iron in the Kupffer cells only, had previously had repeated blood transfusion, and this is in agreement with other workers who have shown that in transfusional haemosiderosis more iron is seen in the Kupffer cells than the hepatocytes (Oliver, 1959). There is no stainable iron in the spleen and myocardium of all the cases with iron in the hepatocytes. Only two cases had moderate amounts of iron in the pancreas.

Haemosiderosis is common in the South African Bantu and this had been associated with large intake of iron derived from the cooking pots (Walker & Arvidson, 1953). However, Gillman & Gillman (1945) studied structural changes in the liver associated with pellagra. They found that hepatic fatty change and haemosiderosis were features of chronic malnutrition in the Bantu adults. Some of these patients were alcoholics and the investigators believed that alcoholism had a role to play in the production of the pellagrous syndrome. Although their study did not include the investigation of pancreatic function it is possible that some of the patients had features of malnutrition secondary to pancreatogenous malabsorption.

In the present study there is no evidence to suggest that haemosiderosis is the result of increased iron intake. Routine autopsy and biopsy material does not indicate that there is significant excess iron deposition in the livers of those who come from the area where the autopsy population is drawn. The rarity of haemosiderosis in Kampala general autopsy population had also been commented on by Davies & Trowell (1951). It is concluded that haemosiderosis in the cases of chronic pancreatic disease is the result of abnormal iron absorption secondary to pancreatic malfunction.

Fourteen out of the fifteen diabetics had no iron in the liver and one with marked amount of iron and fatty change also had clinical malabsorption. This is more evidence to show that impaired exocrine function is a necessary factor for excess iron absorption. Further, all the other cases without iron in the hepatocytes had no clinical evidence of exocrine impaired

function. Thus, there is sufficient evidence to show that the presence of significant amounts of iron and fat in hepatocytes is almost pathognomonic of pancreatigenous malabsorption.

ACKNOWLEDGMENTS

I thank Professor M. S. R. Hutt and Professor R. A. B. Drury for their valuable advice in the preparation of this paper.

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