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PATHOLOGICAL STUDY OF THE LIVER IN KWASHIORKOR*

BY

N. K. CHANDA, M.D., D.C.H.
Medical College, Calcutta

[WITH SPECIAL PLATE]

In Calcutta a syndrome is frequently seen in children which presents a picture of severe malnutrition characterized by diarrhoea, wasting, oedema of varying degree without gross albuminuria, glossitis, anaemia, cutaneous changes with black pigmentation, enlargement of the liver, hypoproteinaemia, eye lesions of vitamin-A deficiency, failure of growth, sometimes mental changes, and anomalies of hair growth (Fig. A). A similar syndrome has also been observed in parts of tropical Africa, and was described under the name "kwashiorkor" by Williams (1933, 1935, 1940). It has also been called infantile pellagra (Trowell, 1937, 1940, 1941), malignant malnutrition (Trowell, 1944; Trowell and Muwazi, 1945a), ariboflavinosis (Hughes, 1946), and fatty liver disease of infants (Waterlow, 1948).

In pathological studies of this syndrome in children in Africa, Williams (1935) and Gillman and Gillman (1944) found only fatty changes of varying degree in the liver parenchyma and no necrosis or haemorrhage. Waterlow (1948) considered fatty change in the liver to be a constant accompaniment of the disease; he also observed increase of fibrous tissue from the portal tracts with a tendency to progress to Laennec's cirrhosis.

In serial biopsies in 120 cases of pellagra, all but two in patients over 10 years of age, Gillman and Gillman (1945) found fatty changes in the liver and cirrhosis. In the adults the cirrhosis was preceded by a deposit of haemosiderin in the portal tracts in fatty livers, giving a picture of haemosiderosis or cytosiderosis. Liver puncture showed that fatty liver is as constant a feature of the syndrome as the rash or oedema, and that it develops early before other known complications such as pneumonia, tuberculosis, or gastro-enteritis. Of the 120 cases investigated, 15 (12.5%) had frankly pigmentary cirrhosis, while in 20% the liver was pre-cirrhotic and about 30% showed signs of serious hepatic damage amounting to cirrhosis. In 1% of cases the liver had no recognizable damage. In none of the livers was there necrosis or haemorrhage. In two cases in children not included in the above series there was irrefutable evidence of non-pigmentary cirrhosis.

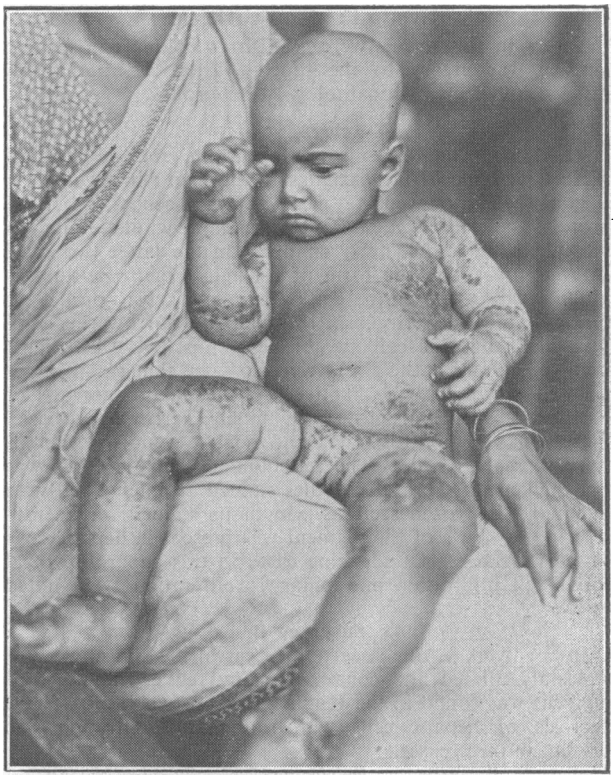


FIG. A.—Typical case of kwashiorkor in Hindu child aged 2 years 2 months. Oedema and skin pigmentation are well shown.

Achar (1950), who studied 78 cases of severe malnutrition in Madras, on histological examination of 12 cases found an extreme degree of fatty infiltration; in two of these cases there was commencing periportal fibrosis, and in one case diffuse fibrosis around the lobules.

The present paper reports the histopathological findings in the liver in 34 cases of kwashiorkor studied post mortem with a view to elucidating the evolution of cirrhosis from hepatic damage.

Method of Investigation

The gross specimens of liver in all cases were fixed in formalin and kept in No. III Kaiserling solution (glycerin and water). After necropsy small pieces of liver tissue 3–5 mm. thick were immersed in Zenker's fluid for 24 hours, washed in running water for 24 hours, and finally preserved in 80% alcohol in tissue jars. Blocks were made by paraffin embedding from different areas of liver in both lobes and studied. Staining methods were as follows: (1) for routine staining—paraffin sections stained by Weigert's iron-haematoxylin and eosin; (2) for connective tissue—Mallory's aniline blue method; (3) for fat—frozen sections stained with Sudan III and counterstained with haematoxylin; (4) for reticulin—Foot and Menard's method as modified by

*Part of the thesis for the M.D.(Calcutta).

Robb-Smith (1937); (5) for the presence of iron pigment—Gillman and Gillman's (1945) modification of Pearl's method.

Cases were classified, according to the histological findings in the liver, into three groups. Group I includes those in which there was an accumulation of fat and/or dilatation of sinusoids but no evidence of cirrhosis. Only one case showed massive necrosis without any fatty change. Group II ineludes cases with pre-cirrhotic changes, and Group III those in which the liver showed definite cirrhosis.

Group I: Non-cirrhotic

Livers in this group were whitish in colour and the cut surface was greasy to the touch. They can be further divided into four histopathological subgroups.

Subgroup A

There were nine cases in this subgroup. The histological picture was one of fatty change in the liver; in seven cases a moderate amount of fat was present, occupying half or more of the cytoplasm, and in two cases the whole lobule was affected with marked fatty change. In the latter two cases fat was present in the form of a single large, pale-staining globule filling the entire cell; the nucleus was pushed to one pole and the cytoplasm reduced to a narrow rim compressed against the cell membrane, almost every cell being involved. In fact the livers were so fatty that small pieces of tissue floated in the fixative. There was no necrosis or haemorrhage. Sinusoids were much narrowed (Special Plate, Fig. 1). Portal tracts and hepatic venous terminals were scarcely visible. The reticulum of hepatic cords was not thickened. The fat globules stained an intense red with Sudan III in frozen sections. In tissue stained for haemosiderin very little of the pigment was present in hepatic cells or portal tracts. Of the nine cases in this subgroup, focal round-cell infiltration and biliary proliferation were noted in five.

Subgroup B

In the livers in this subgroup (7 cases) the sinusoids were markedly dilated and contained many red cells. Malarial pigment was found in the Kupffer cells in two cases. Focal necrosis of hepatic cells with round-cell infiltration was present in three cases.

Subgroup C

Livers in this subgroup showed a combination of varying degrees of fatty change with dilatation of sinusoids (Special Plate, Fig. 2). The sinusoids contained red cells. Of the four cases in this category two had coexistent tuberculous infection; in another case there were small areas of focal necrosis in the parenchyma with infiltration of round cells.

Subgroup D

In this subgroup there was only one case, in a Hindu boy aged 2 years whose illness had lasted seven months. The liver weighed 350 g.; it was yellowish-white in colour and of normal consistency. Microscopically, it showed massive necrosis of the hepatic cells so extreme that normal hepatic cords could be found only after prolonged search. The destruction had involved large areas so that there was no zonal distribution of the necrosis. In the affected areas the cells had lost their nuclei; the sinusoids were dilated and contained red cells, many polymorphonuclear leucocytes, and histiocytes (Special Plate, Fig. 3). The biliary tree showed extreme proliferation. The ducts were enormously dilated, producing cystic spaces lined by cuboidal cells with hyperchromatic nuclei. The cells had proliferated and been thrown into folds. The proliferated bile capillaries lay in an oedematous acellular connective tissue. Cells did not show any fatty change. Reticulin stain revealed destruction of reticulum of the hepatic lobules, and with specific connective-tissue stain an increase in collagen fibres in between proliferated bile capillaries was noted.

Group II: Pre-cirrhotic

In this group are included the eight cases in which there were pre-cirrhotic changes in the liver. The lobules showed moderate to marked fatty changes combined with a varying degree of dilatation of sinusoids, which were filled with red cells. Fibroblastic connective tissue was seen arising from the portal tracts and spreading into the liver parenchyma without connecting up the portal tracts, resembling an early stage of cirrhosis. The connective tissue was infiltrated with lymphocytes and there was proliferation of the biliary tree. Staining of the tissue for haemosiderin showed none present in the hepatic cells or portal tracts.

In three of the cases the liver tissues showed focal areas of necrosis without specific zonal distribution; bile-duct proliferation was also present. Evidence of coexistent tuberculous infection was found in two cases.

Group III: Cirrhotic

This group comprises cases in which the liver showed a definitely established cirrhotic condition. These are further subdivided according to whether the cirrhosis was (A) post-infiltrative or (B) post-necrotic.

Subgroup A

There were four cases showing definite cirrhosis of post-infiltrative type.

Case 1.—A Hindu boy of 4 who had had the disease six months. The liver weighed 490 g.; it was pale yellow in colour, with a slightly granular surface and firm consistency (Fig. B). Microscopically, thin bands of cellular fibrous tissue extending from the portal tracts had encircled masses of liver cells, isolating them into lobules, the encirclement being complete in some places and incomplete in others. The hepatic cells showed extreme fatty changes, and the sinusoids in the central and mid-zonal areas of the lobule were greatly dilated and filled with red cells (Special Plate, Fig. 4). In some of the hepatic cells a brownish bile pigment was present. In the portal tracts the fibrous tissue was increased and infiltrated with lymphocytes. The hepatic artery and portal veins were normal. The bile ducts were healthy, their lumen being patent and the lining epithelial cells intact and normal. There was some proliferation of the biliary canaliculi in the region adjacent to the portal tracts. The central veins were normal, and no endophlebitis or thickening was found. Staining of reticulum of the sinusoids showed the sinusoidal capillary bed of the lobules to be normal. Specific connective-tissue stain showed adult connective tissue with monolobular distribution arising from the portal tracts (Special Plate, Fig. 4).

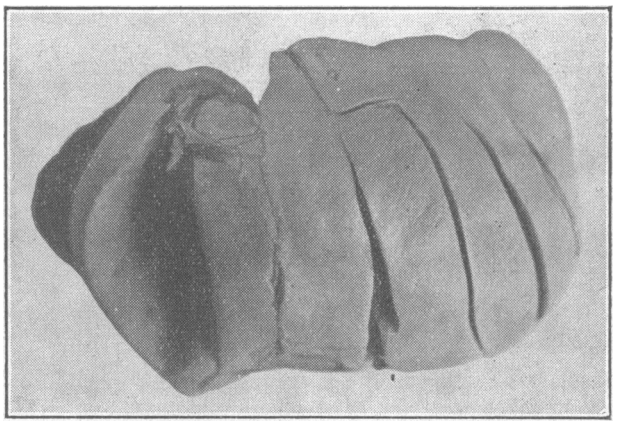


FIG. B.—Liver from Case 1.

Case 2.—A Hindu aged 4 years with a history lasting 1½ years. The liver weighed 200 g.; it was pale yellow in colour, and had a smooth surface and slightly firm consistency. Microscopically, cellular connective tissue extending from the portal tract had encircled masses of liver cells around each lobule, resulting in monolobular cirrhosis. The hepatic cells showed varying degrees of fatty change, and the sinusoids were dilated and filled with red cells. There was no necrosis of the hepatic cells. The central veins were

thickened in places, but without endophlebitis or thrombosis, while in some places they were dilated. No evidence of regeneration of parenchyma was seen.

Case 3.—A Hindu girl aged 1 year with a history of six months' duration. Microscopically, the portal tract showed increased fibrous tissue from Glisson's capsule. There was moderate lymphocytic infiltration, also biliary proliferation around the portal tracts and the fibrous tissue spreading from them. The hepatic artery, portal veins, and bile ducts were normal. The hepatic venous tree was also normal. Silver impregnation of the sinusoidal capillary bed showed a normal reticular pattern in a sinusoidal capillary arising from collagenous tissue of the portal tracts. Staining for haemosiderin was negative in the portal tracts and hepatic cells.

Case 4.—A Hindu male infant aged 5 months. The liver weighed 12 g.; its colour yellowish white, surface smooth, consistency slightly firm. Microscopically, a vascular connective tissue from the portal tracts surrounded the liver lobule, resulting in monolobular cirrhosis (Special Plate, Fig. 5). The hepatic cells showed varying degrees of fatty change in the periphery of the lobule. There was no necrosis. In the central and mid-zonal areas of the lobule the sinusoids were dilated and filled with intact red cells. There was no evidence of regeneration of the hepatic parenchyma. The fibrous tissue from the portal tracts showed moderate lymphocytic infiltration and biliary proliferation.

Comment.—The four cases in this subgroup show monolobular cirrhosis in an extremely fatty liver. No evidence of regeneration of parenchyma was seen.

Subgroup B

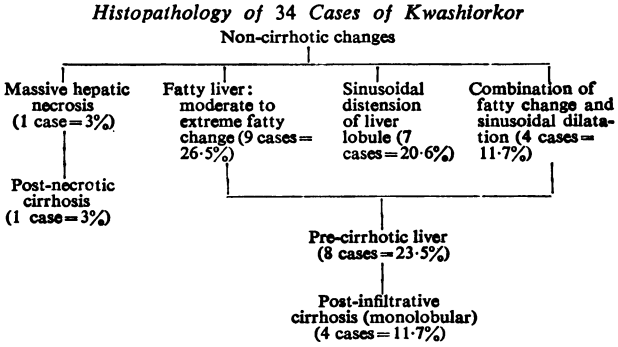
Only one case belonged to this subgroup—that of a Hindu male infant aged 5 months. The liver weighed 150 g., and was yellowish-green in colour, firm in consistency, and with a finely granular surface. Microscopically, fibrous tissue spreading from the portal tracts had surrounded single lobules, resulting in monolobular cirrhosis, while in places there was only increase of fibrous tissue from the portal tracts. The hepatic cells showed complete necrosis with granular acidophilic cytoplasm, nuclei in most areas having completely disappeared (Special Plate, Fig. 6). The necrotic cells contained bile pigment scattered throughout the cytoplasm. Fibrosis had spread from the portal tracts and was slightly infiltrated with lymphocytes; in places the connective tissue was acellular. The portal tracts were difficult to distinguish. Silver impregnation of reticular fibres of the hepatic parenchyma showed thickening of these fibres in the hepatic lobules spreading from collagenous tissue of the portal tracts. Mallory's aniline blue stain showed mature collagenous tissue spreading from the portal tracts, resulting in monolobular cirrhosis; in places fibrous tissue had entered the hepatic lobules. Staining for the presence of haemosiderin failed to demonstrate its presence in portal tracts or hepatic lobules.

Comment.—The picture is one of subacute massive hepatitis leading to post-necrotic cirrhosis.

Discussion

The histopathology has been studied in 34 cases of kwashiorkor in an attempt to follow the development of cirrhosis in this condition. Of the 34 cases, nine (26.5%) showed only fatty change (moderate to extreme in degree), seven (20.6%) sinusoidal dilatation of the liver lobule, and four (11.7%) a combination of fatty change and sinusoidal dilatation. A further eight cases (23.5%) showed a pre-cirrhotic condition of the liver with dilatation of sinusoids and moderate fatty change, and four (11.7%) a definite cirrhotic condition, monolobular in type. No haemosiderin could be detected by special staining of iron in liver tissue. On the other hand, one case showed massive hepatic necrosis and one case post-necrotic cirrhosis. The results of the study can be summarized as follows:

Histopathology of 34 Cases of Kwashiorkor



Pathological studies of kwashiorkor (Williams, 1933; Gillman and Gillman, 1944) have indicated that fatty change is a constant accompaniment of the disease. Gillman and Gillman (1945), from serial biopsies in 120 cases of pellagra, a syndrome resembling kwashiorkor, observed fatty change progressing to frank pigmentary cirrhosis in 12.5% of cases. In two children not included in the 120 cases the liver showed irrefutable evidence of non-pigmentary cirrhosis.

In the present investigation the fatty liver of kwashiorkor was found to have progressed to Laennec's cirrhosis in 11.7% of the 34 cases, the cirrhosis being of non-pigmentary type. Although four cases in the series showed definite post-infiltrative cirrhosis and one case a post-necrotic cirrhosis, ascites was clinically evident in only two cases. Again, jaundice was not found clinically in any of these five cases. Nine of the 22 cases in Group I (non-cirrhotic) belonged to Subgroup A. In all nine cases cells of the hepatic lobule showed moderate to extreme fatty change with much-narrowed sinusoids. This observation is in conformity with the findings of Gillman and Gillman (1945) in pellagrins in Africa, both infants and adults. Eight cases in the present series showed pre-cirrhotic changes. There were four cases with post-infiltrative cirrhosis, all of them showing fatty change at the periphery of the lobule, while the sinusoids in the central and mid-zonal regions were dilated.

In man fatty liver as a precursor of Laennec's cirrhosis was first observed by Connor (1938) in diabetics. This observation stimulated the study of experimental Laennec's cirrhosis, which showed that prolonged fatty infiltration due to a deficient or unbalanced diet leads to cirrhosis (Rich and Hamilton, 1940; Himsworth and Glynn, 1944a; Chaikoff *et al.*, 1940, 1943). In the present series of 34 cases of kwashiorkor four cases showed post-infiltrative fatty monolobular cirrhosis. Although it may be true that prolonged fatty infiltration leads to cirrhosis, there may be other factors in addition to the fatty infiltration which help the progression to cirrhosis, as has been suggested by Walters and Waterlow (1954), but what these are we do not know.

One case in the present series showed massive hepatic necrosis (Special Plate, Fig. 3) and another had post-necrotic cirrhosis (Special Plate, Fig. 6). Pathological study of the liver by Williams (1933) in kwashiorkor and by Gillman and Gillman (1945) in pellagra showed the absence of necrosis or haemorrhage. Glynn, Himsworth, and Neuberger (1945) have demonstrated experimentally in rats that deficiency of cystine leads to massive hepatic necrosis, the survivors developing post-necrotic scarring and nodular hypoplasia. The inference is that dietetic deficiency of casein causes deficiency of cystine, leading to massive necrosis and post-necrotic scarring. From this it would seem reasonable to suggest that in man severe malnutrition may lead to deficiency of cystine and its effect—massive hepatic necrosis with its sequel post-necrotic scarring.

Again, of the group with non-cirrhotic livers, seven cases showed only dilatation of sinusoids and four showed a combination of dilatation of sinusoids with fatty change. In the eight cases with pre-cirrhotic livers and the four in which there was cirrhosis slight dilatation of sinusoids was also observed. In studies of the pathology of kwashiorkor by Williams (1935) and of infantile pellagra by Gillman and

Gillman (1945) dilatation of sinusoids was never observed; on the other hand, in all fatty livers sinusoids were closed. Gillman, Gillman, Mandelstam, and Gilbert (1945), in rats fed on a diet of mealie pap, the staple food of African children, observed dilatation of sinusoids as a separate pathological finding occurring independently of fatty change and cirrhosis. The finding of dilatation of sinusoids in the present series is a new observation in connexion with studies in human beings.

Out of the 34 cases, in two cases histological examination showed the presence of malarial haemozoin pigment in Kupffer cells, and in four cases there was evidence of tuberculous infection. These are coexistent lesions and play no part in the pathogenesis of the disease.

There are grounds for suggesting that in kwashiorkor there may be deficiency not only of choline but also of both methionine and cystine, resulting in massive necrosis and post-necrotic cirrhosis, though the latter is of rare occurrence (3% in the present series). Although histologically there is fibrosis of the liver in this syndrome, producing a typical picture of cirrhosis, this usually does not present as fully developed cirrhosis with hepatocellular dysfunction and portal obstruction such as is seen in infantile cirrhosis of Indian children, in which the histological picture is different, and has been described by Rao (1935) as subacute toxic cirrhosis.

Summary

Study of the histology of the liver in children suffering from kwashiorkor shows the evolution of cirrhosis from fatty change (post-infiltrative cirrhosis). This is a separate entity of cirrhosis, clinically and pathologically, distinct from the commonly occurring infantile biliary cirrhosis as described by Gibbons (1883, 1890).

Other than fatty change in the liver in kwashiorkor, dilatation of sinusoids may be the only pathological change. Very rarely there may be massive hepatic necrosis and post-necrotic fibrosis.

The clinical part of this work was carried out in the Medical College Hospitals, and the work on morbid anatomy and histology in the Department of Pathology, Medical College of Calcutta. I am indebted to the Principal and Superintendent, Medical College Hospitals, for constant help and kind encouragement.

I offer my sincere and grateful thanks to Dr. B. P. Tribedi, late Professor of Pathology, Medical College, Calcutta, for his constant help and encouragement in carrying out this work. My grateful thanks are also due to the staff of the Department of Pathology for their ungrudging help.

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THE RENAL LESION IN ANGIOKERATOMA CORPORIS DIFFUSUM

BY

J. R. COLLEY, M.B., B.S.

D. L. MILLER, M.B., B.Chir.

M. S. R. HUTT, M.D., M.R.C.P.

H. J. WALLACE, M.D., F.R.C.P.

AND

H. E. de WARDENER, M.D., M.R.C.P.

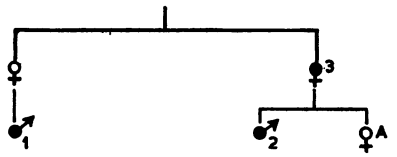
From St. Thomas's Hospital and Medical School, London, S.E.1

[WITH SPECIAL PLATE]

Angiokeratoma corporis diffusum is a rare disorder first described by Fabry in 1898. About 30 cases have been reported. The literature has been well reviewed by Fessas *et al.* (1955). The disease appears to have a familial incidence and has been reported only in males. It is characterized by multiple small angiokeratotic lesions in the skin, which usually first appear during late childhood. It is also associated with diminished sweating, pains in hands and feet, ankle oedema, proteinuria, renal failure, and hypertension.

Frozen sections demonstrate that there is generalized deposition of a doubly refractile substance; it is found particularly in the smooth muscle cells of the arteries and the heart. It has also been found in the ganglion cells of the brain, lymph nodes, spleen, bone marrow, and kidneys; cells containing a doubly refractile substance have also been found in the urinary deposit. In fixed tissues the cells containing this substance appear distended and vacuolated.

Two further cases of the disease in males in one family are described with particular reference to the renal biopsy findings. A third, female, member of the same family in whom identical renal lesions were found at necropsy is also reported. The three patients (shown in black) are related as follows:



A description of the histological lesions in all three cases follows the case histories.

Case 1

This patient, aged 38, was first seen in September, 1956, complaining of headaches. He had had six attacks of migraine during the preceding year and an occipital headache for two weeks. For three years he had had a noticeable thirst, with nocturia for about three months. Slight ankle oedema had been present for one year. The skin abnormality had been present for as long as he could remember.

Examination

He was a healthy-looking man of normal intelligence. The skin was dry, and on the buttocks, scrotum, penis, medial aspects of thighs, knees, and elbows there were small elevated purple lesions, the smallest about 1 mm. in

N. K. CHANDA: LIVER IN KWASHIORKOR

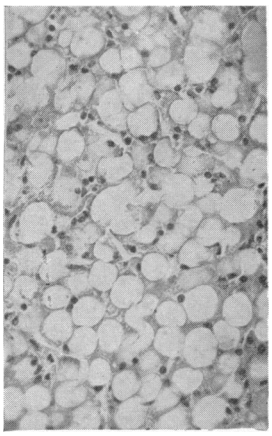


FIG. 1.—Section of liver of Group I, Subgroup A, showing extreme fatty change of liver cells; the sinusoids are collapsed and empty. (H. and E. ×255.)

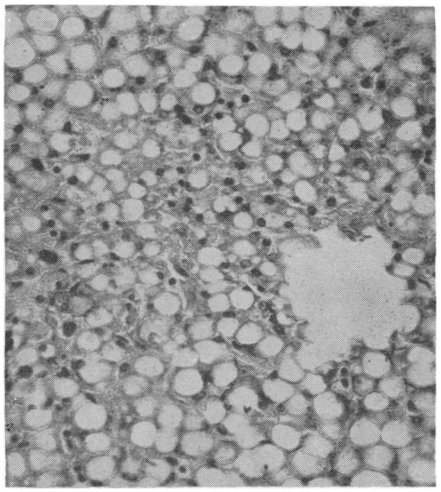


FIG. 2.—Section of liver of Group I, Subgroup C, showing fatty change in liver cells and dilatation of sinusoids; central vein also much dilated. (H. and E. ×144.)

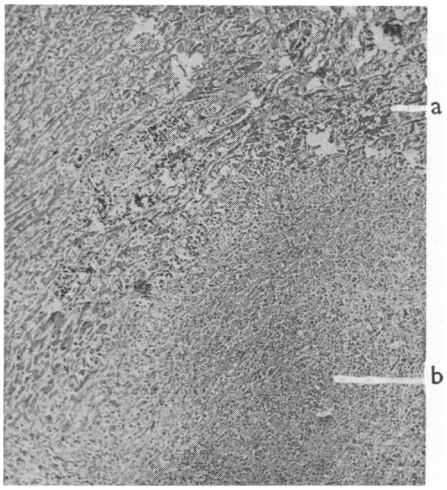


FIG. 3.—Section of liver showing (*a*) few hepatic cords in upper half; (*b*) necrosis of hepatic cells and infiltration with neutrophils and histiocytes in lower half. (H. and E. ×70.)

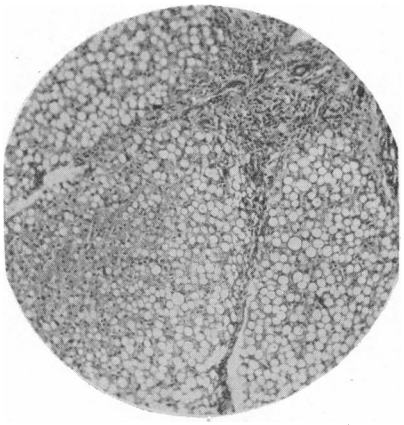


FIG. 4

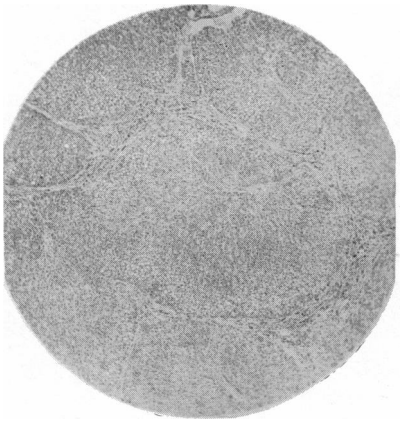


FIG. 5

FIG. 6

FIG. 4.—Case 1. Section of liver showing: fibrous tissue spreading from portal tracts, resulting in monolobular cirrhosis; liver cells with fatty change at periphery of lobule; and dilatation of sinusoids in centre of lobule. (H. and E. ×88.)

FIG. 5.—Case 4. Section of liver showing monolobular distribution of fibrosis. Hepatic lobules show dilatation of central vein and sinusoids in central and mid-zonal areas, fatty change in liver cells in peripheral zone, and lymphocytic infiltration and biliary proliferation of fibrous tissue. (H. and E. ×44.)

FIG. 6.—Section of liver showing necrosis of hepatic cells and monolobular distribution of fibrosis. (H. and E. ×44.)

J. R. COLLEY *ET AL.*: RENAL LESION IN ANGIOKERATOMA CORPORIS DIFFUSUM

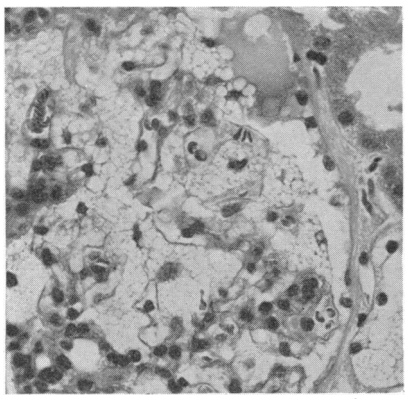


FIG. 1.—Portion of glomerulus from Case 2 showing "honeycomb" appearance due to distension and vacuolation of epithelial cells of tuft. An adjoining distal tubule cell shows the same appearance. (H. and E. ×305.)

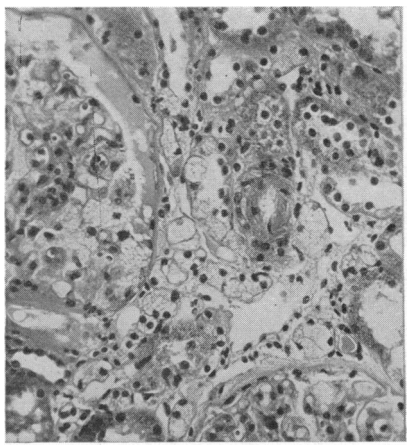


FIG. 2.—"Honeycomb" glomeruli with similar vacuolation of adjacent tubules. (H. and E. ×170.)

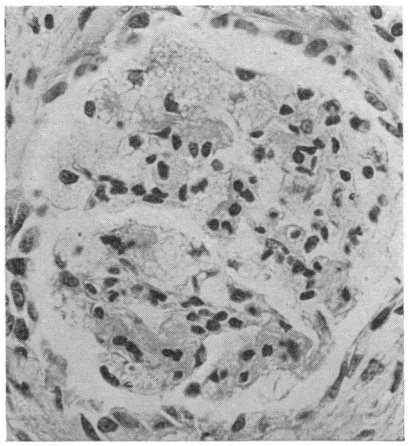


FIG. 3.—"Honeycomb" glomerulus from Case 3 with early periglomerular fibrosis. (H. and E. ×305.)