ACTIVE CHRONIC HEPATITIS ASSOCIATED WITH RENAL TUBULAR ACIDOSIS AND SUCCESSFUL PREGNANCY

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Recently a number of authors (Waldenstrom,[1] Bearn *et al.*,[2] Willcox *et al.*[3]) have described a chronic progressive form of liver disease usually occurring in young adults and characterized by icterus, hepatosplenomegaly, a histologic picture of hepatic parenchymal cell damage, massive fibrosis and portal lymphocyte infiltration, hypergammaglobulinaemia (2·0 G/100 ml. or higher) and elevated serum transaminase levels. Mackay *et al.*[4] termed this condition 'lupoid hepatitis'; Page and Good,[5] judging from the hepatic histologic picture used the term 'plasma cell hepatitis', while Read *et al.*[6] called it 'juvenile' cirrhosis. Most recently Sheila Sherlock[7] has suggested the name 'active chronic hepatitis'.

This paper describes an instance of its association with renal tubular acidosis (RTA) and suggests the role of autoimmunity in their pathogenesis.

CASE REPORT

First Admission

A Bantu female, aged 21 years, was admitted in January 1963 with an 8-month history of jaundice, generalized itching and amenorrhoea. She had received no drugs previously. There was evidence of scratching on the skin and enlargement of liver and spleen.

Investigations. Serum albumin 3·4, serum globulin 4·9, serum gammaglobulin 2·0 G/100 ml., haemoglobin 12·0 G/100 ml., white cell count 6,000/cu.mm., blood urea 25 mg./100 ml. The stools were stercobilin free. The urine contained a trace of protein and 10 leucocytes/high-power field and culture yielded a heavy growth of *B. coli*. There was bilirubinuria without increase in urobilin. Other relevant biochemical find-

ings are shown in Table I. X-ray examination of the abdomen showed calcification in the region of the right kidney and intravenous pyelography (Fig. 1) confirmed that multiple calculi were present in the right renal pelvis, which was hydronephrotic.

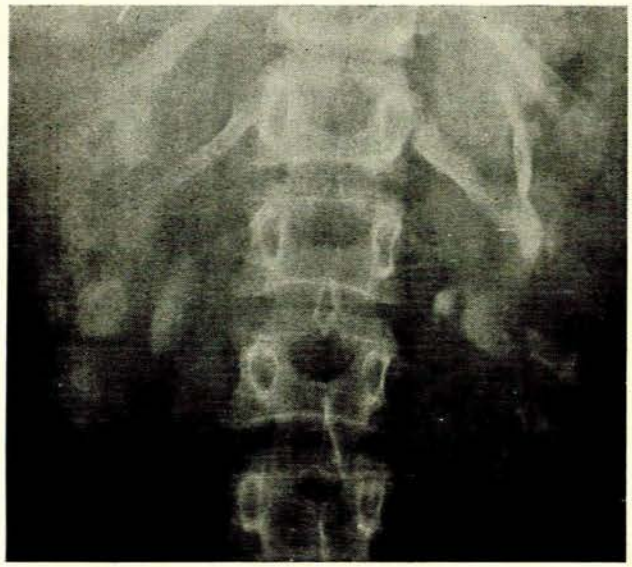

Fig. 1. Intravenous pyelogram. Multiple calculi are present in the right renal pelvis which is hydronephrotic.

A biopsy specimen of the liver (April 1963) was reported to show 'irregular fibrosis and distorted structure. There is rather diffuse inflammatory infiltration including a few plasma cells. Cholestasis is heavy.' The patient was treated with 60 mg. of prednisone daily, the serum bilirubin dropping to 2·4 mg./100 ml. After 6 weeks she left hospital against advice and steroids were discontinued accordingly.

TABLE I. BLOOD INVESTIGATIONS

	Serum bilirubin (mg./100 ml.)	*Serum alkaline phosphatase (KA units/100 ml.)*	*Serum cholesterol (mg/100 ml.)*	*SGOT (units/ml.) (normal 0-40 units/ml.)*
First admission	17·6	28	850	80
During pregnancy	20·0	50	830	92
After pregnancy	12·0	25	830	80

Re-admission

She was re-admitted 10 months later complaining of increasingly intense pruritus and was found to be 20-weeks pregnant and deeply icteric. The hepatosplenomegaly was unchanged.

Investigations. Urine pH 6·0 and protein free with 2 red cells/high-power field; haemoglobin 9·1 G/100 ml., white cell count 6,000/cu.mm., platelet count normal, blood smear showed a normocytic normochromic anaemia with numerous target cells; serum calcium and phosphorus were within normal limits; LE cells were not found in 3 preparations; the latex fixation test was positive and thyroid antibodies were detected in the serum using the gel diffusion-precipitation technique as described by Roitt and Doniach.[8] Liver biopsy showed 'heavy dense fibrosis, but in some places piecemeal necrosis and cellular infiltration are present. Cholestasis is again heavy' (Fig. 2).

Throughout pregnancy 30 mg. of prednisone was given daily without appreciable effect on the serum bilirubin or alkaline phosphatase levels. The patient delivered spontaneously at the 30th week of pregnancy. There was no malformation in the infant who was deeply jaundiced, the serum bilirubin being largely unconjugated.

In the puerperium further investigation showed the CO_2 content of the plasma to be 19·3 mEq./l.; urine pH 7·0; serum sodium 141, serum potassium 3·6, serum chloride 106 mEq./l. On loading with ammonium chloride (6 G daily for 4 days) the plasma CO_2 content dropped to 16·2 mEq./l. and the urine pH reached 6·5 confirming the existence of RTA. The titratable acidity of the urine was 25 mEq./l./24 hours (normal 125 - 200 mEq./l./24 hours). There was no abnormal aminoaciduria on paper chromatography. The direct Coomb's test was positive; the cold agglutinin titre was within normal limits and there was a weak non-specific auto-antibody present which was consistent with erythrocyte autosensitization. At exploratory laparotomy the liver was described as enlarged with a smooth surface; the spleen was enlarged. Extrahepatic biliary obstruction was excluded. A wedge of liver tissue taken at laparotomy for biopsy showed 'lobular structure normal, and there was no fibrosis. Portal inflammation is very mild. Cholestasis is heavy.'

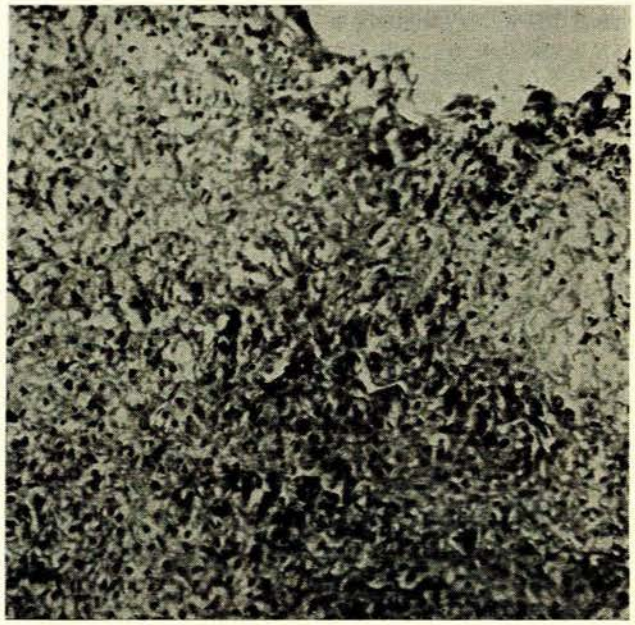

Fig. 2. Biopsy specimen of the liver. Heavy dense fibrosis, piecemeal necrosis and cellular infiltration are present.

DISCUSSION

Certain features in this case are consistent with a diagnosis of 'active chronic hepatitis': the age of the patient, the icterus, the hepatomegaly with characteristic hepatic histology, the splenomegaly, hypergammaglobulinaemia and elevated serum transaminase levels. The duration of the illness suggests a late phase of the disease. Alternatively the picture is consistent with a chronic persistent hepatitis, with marked cholestasis, following viral hepatitis.

Renal calculi are uncommon in the Bantu in Natal (Wise and Kark,[9] Coetzee[10]). Since Wrong and Davies[11] found nephrocalcinosis in 73% of their patients with RTA it is possible that in this case the renal calculi were related to RTA.

The persistence of urine pH over 5·7 and the development of a metabolic acidosis after loading with ammonium chloride, satisfy Randall and Targgart's[12] conditions for the diagnosis of RTA. Huth *et al.*[13] in their classifi-

cation of the causes of RTA do not mention autoimmunity. A genetic study as reported by Randall and Targgart[12] and Seedat[14] was not done in this case, but there was no family history of symptoms referable to RTA. Albright *et al.*[15] considered pyelonephritis to be a cause of RTA. However, as suggested by Huth *et al.*[13] the pyelonephritis in this patient probably resulted from, not in, nephrolithiasis.

Read *et al.*[6] in their paper on 'juvenile' cirrhosis found a patient with RTA and another with nephrocalcinosis at necropsy. In 3 cases the syndrome of polyuria, thirst and hypokalaemia was present. They state that 'renal disease complicating liver disease is well recognized', and cite as forms of renal disease associated with 'juvenile' cirrhosis, lupus nephritis (Taft *et al.*[16]), chronic nephritis (Willcox and Isselbacher[3]) and transient albuminuria (Page and Good[5]). It is possible that the hepatic and renal lesions in the present case are the result of an autoimmune mechanism in view of the positive latex fixation test (Bouchier *et al.*[17]), hypergammaglobulinaemia (Read *et al.*[6]), positive antiglobulin Coomb's test and presence of thyroid antibodies in the serum (Roitt *et al.*[18]).

Amenorrhoea and infertility are usual in 'active chronic hepatitis' and successful pregnancy has rarely been recorded (Slater;[19] Bearn *et al.*;[2] Joske *et al.*[20]). Hepatic function deteriorated during pregnancy in the present case, as reflected in the serum bilirubin and alkaline phosphatase levels.

SUMMARY

A case of 'active chronic hepatitis' associated with renal tubular acidosis is described. The possibility of an autoimmune mechanism underlying both lesions is suggested. Another instance of successful pregnancy in 'active chronic hepatitis' is recorded.

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