INCREASED MITOTIC ACTIVITY IN THE LIVER AND OTHER ORGANS IN A CASE OF ACUTE RENAL TUBULAR NECROSIS

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A case is presented in which numerous mitotic figures were found in the liver, pancreas, and adrenal glands of a patient who died in uraemia due to acute tubular necrosis.

The possibilities of the failure of excretion of a waste product acting as a stimulus to mitosis, or that a mitotic stimulant is released from the acutely ischaemic kidney, are suggested.

The mitotic index of the adult mammalian liver is low (Brues and Marble, 1937; Swann, 1958). Increased mitotic activity is seen in the liver in cases of acute hepatic necrosis, and in the experimental animal mitotic division is a prominent feature in the liver remnant after partial hepatectomy (Higgins and Anderson, 1931).

Bullough (1950) has clearly demonstrated in epidermal cells in the mouse that no cells enter prophase after the animal's death, but that cells which have begun dividing in the living animal will complete their division. If this were true for the human liver cell, one would expect to find no mitoses in the liver at necropsy except in cases where the examination was performed shortly after death. However, mitotic figures are seen after death in cases of acute hepatic necrosis and occasionally they are seen in livers in which morphological evidence of liver damage is absent.

Case Report

L. T., a Bantu boy aged 15 years, was admitted with a history of frontal headache and unproductive cough for four days. Six days previously he had experienced nausea associated with abdominal pain, but this had resolved spontaneously. He had had no diarrhoea. The only other important point in the history, obtained on direct questioning, was that he had last passed urine three days before admission.

On examination, the patient was well nourished and did not appear to be acutely ill. The blood pressure on admission was 120/80 mm. Hg. No abnormality was detected in the cardiovascular or respiratory systems. The liver was palpable 1 in. below the right costal margin. Systemic examination revealed no further significant findings.

The patient passed a small quantity of urine shortly after admission and this contained a moderate amount

of albumin and numerous granular, epithelial, and red cell casts.

The clinical diagnosis was acute glomerulonephritis and he was treated with antibiotics and maintained on a restricted oral fluid intake.

On the second morning after admission he had passed 6 oz. urine during 24 hours and his blood pressure was 130/90 mm. Hg. Shortly after being seen he had a generalized epileptiform convulsion and died.

Necropsy Findings

Necropsy was performed 24 hours after death.

The body was that of a well-nourished Bantu male (height 5 ft. 6½ in.).

The heart weighed 320 g. but showed no further abnormality. There was an acute tracheo-bronchitis with a resolving bronchopneumonia in the lower lobe of the left lung.

The kidneys weighed 260 and 280 g. The capsules stripped easily, leaving smooth, pale surfaces. The cortices were swollen and pale and the vascular markings were indistinct. Histologically both proximal and distal convoluted tubules were dilated and the lining epithelium was flattened. These changes were most prominent in the distal convolutions. Scattered cells in the distal convolutions and in the loops of Henle showed degeneration and necrosis. Focal tubulorrhexis was present. The tubular lining epithelium showed widespread signs of regeneration (Fig. 1). Many distal convoluted and collecting tubules and many of the loops of Henle contained red granular and haemoglobin casts and desquamated, sometimes necrotic, epithelial cells. Numerous names have been suggested for this lesion, but acute tubular necrosis seems to be the

FIG. 1

FIG. 1.—Dilated distal convoluted tubules in the kidney, containing granular casts and showing evidence of regeneration of the epithelium. Haematoxylin and eosin $\times 1,000$.

FIG. 2.—Section of the liver showing a large multinucleate liver cell. Haematoxylin and eosin $\times 1,000$.

most satisfactory one at present (Sevitt, 1959). The aetiology of the lesion is uncertain in this case. (No primary glomerular lesion was noted.)

The liver weighed 1,860 g. and appeared macroscopically normal. On histological examination an occasional bilharzial granuloma was seen. The lobular pattern was preserved and the portal tracts and small bile ducts showed no abnormality. Mild to moderate nuclear polyploidy was present and there were many binucleate cells as well as a moderate number of tri- and multinucleate liver cells (Fig. 2). Numerous mitoses were distributed through-

FIG. 2

FIG. 3.—Three mitoses in a small field in the liver. Haematoxylin and eosin $\times 2,500$.

FIG. 4.—Section of liver showing a large tripolar metaphase. Haematoxylin and eosin $\times 2,500$.

FIG. 5

FIG. 6

FIGS. 5-7.—Liver cell nucleus in prophase (Fig. 5), in metaphase (Fig. 6), and in anaphase (Fig. 7). Haematoxylin and eosin $\times 2,500$.

out the liver lobules (15/1,000 liver cell nuclei (Fig. 3) in counts of tissue sections). Several abnormal mitoses were present (2-3%) and those mostly took the form of tripolar spindles (Fig. 4). Some of the metaphases were large and suggested polyploid cells in mitoses. All phases of the cycle were represented, but metaphases predominated (Figs. 5-7), the proportions being prophase 5%, metaphase 80%, anaphase 13%, and telophase 2%.

The spindles in metaphase and anaphase were easily visible in sections stained with haematoxylin and eosin, but appeared otherwise morphologically normal. Neither fat nor glycogen could be demonstrated in suitably prepared and stained sections of liver.

Some mitotic figures were seen in the acinar and islet cells of the pancreas and in the cortex of the adrenal gland, chiefly in the zona fasciculata.

Discussion

Whether the mitotic figures represented a true increase in mitotic activity or a delay in the mitotic cycle is difficult to say on histological grounds alone. Complete inhibition of the mitotic cycle was unlikely as all phases are represented. A phase count on a liver biopsy from a case of viral hepatitis, in which many mitotic figures were present, showed a similar distribution (prophase 6%, metaphase 80%, and anaphase 14%). Also the presence of tri- and multinucleate liver cells suggested a true increase in mitotic activity.

Paget (1954) has shown that in post-mortem liver sections, excluding those from cases of liver disease, mitoses are seen almost exclusively in patients dying in acute or subacute uraemia. Bywaters (1946) found mitoses in the liver in 10 of 42 cases of traumatic anuria, and in two of the cases no evidence of necrosis was seen in the liver.

As a result of the striking mitotic activity in this case and the report by Paget, we are at present reviewing a consecutive series of post-mortem liver sections and the livers of 50 cases of acute tubular necrosis. Preliminary results confirm Paget's findings and show a correlation between mitotic activity in morphologically normal livers and the renal lesion in cases of acute uraemia (acute tubular necrosis). In attempting to explain the association with acute and not chronic uraemia, Paget felt that necrosis may be the

important factor. Our case did not show extensive cellular necrosis, and necrosis is frequently not a marked feature in this type of renal lesion (Brun and Munck, 1957). Bywaters suggested that the mitoses represented a reparative response to functional damage to liver cells as a result of anoxia. Acute renal ischaemia appears to be the underlying factor in the production of the renal lesion (Sevitt, 1959). Although this is associated in many cases with a generalized state of shock, vasoconstriction and ischaemia are often more marked in the kidney than elsewhere in the body (Lauson, Bradley, and Cournand, 1944). Local anoxia may, therefore, not always be a marked feature in the liver.

Our case showed mitoses in the pancreas and adrenal cortex, and Bywaters found mitoses in other organs in two of his cases (kidney and pancreas in one and kidney and thyroid gland in another). This suggests the possibility of a humoral effect. It has been suggested (Swann, 1958) that the stimulus for mitosis in the remaining kidney after unilateral nephrectomy is the failure of excretion of a waste product and a similar mechanism may operate in acute renal shutdown. On the other hand, the common denominator in this type of case may be the renal lesion itself (acute tubular necrosis). It could then be postulated that either an inhibitor is no longer formed or a specific substance is released from the kidney in acute renal ischaemia which stimulates mitotic division in the liver and other organs, including, when the acute vasoconstrictive phase has passed, the renal tubular epithelial cells.

Further work on this problem may elucidate one of the mechanisms involved in mitotic stimulation or inhibition.

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