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COLLAGEN RESORPTION BY HEPATOCYTES DURING REGRESSION OF CIRRHOSIS OF THE LIVER

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The possibility of regression of cirrhosis of the liver has been conclusively proved by many investigations [1, 2]. The study of this problem is now concentrated mainly on elucidation of the mechanism of resorption of sclerotic tissue. Since collagen destruction in the liver is considered to take place entirely extracellularly, most research has been devoted to a study of the role and degree of participation of collagenase in this process [4-8]. It is not known whether hepatocytes participate in collagen resorption and, if they do, how this participation is manifested.

In the investigation described below an electron-microscopic method was used to study the liver in experimental cirrhosis and its regression. Attention was concentrated on hepatocytes which, according to the writer's observations, play an important role in the resorption of sclerotic tissue.

EXPERIMENTAL METHOD

Noninbred male albino mice were used. Cirrhosis of the liver was induced by injection of 0.2 ml of a 40% solution of CCl_4 in olive oil into the animals subcutaneously once a week for 5 months. To stimulate regeneration, 10 days after the last injection of CCl_4 all the animals underwent resection of the left lobe of the liver. Partial hepatoectomy has been shown [1, 3, 9] to accelerate regeneration of the cirrhotically changed liver considerably. Material for study was taken during resection and 5, 10, and 15 days thereafter. Material for histological investigation was fixed in 10% formalin, for electron microscopy — in OsO_4 or glutaraldehyde, followed by postfixation in OsO_4, dehydrated, and embedded in Epon. Serial ultrathin sections were cut (50-60 from each block) and examined in the ÉMV-100L electron microscope.

EXPERIMENTAL RESULTS

A picture of cirrhosis with annular proliferation of connective tissue and the formation of pseudolobules was observed in histological sections from pieces of liver removed during resection. Electron microscopy revealed bundles of collagen fibers of different thickness, with clearly distinguishable characteristic cross striation. Lipid inclusions were present in the cytoplasm of most hepatocytes. Far fewer lipid inclusions, but many lysosomes and peroxisomes were present 5 days after resection in the hepatocytes and the lamellar complex was well developed. Some bands of fibers 10 days after partial hepatectomy consisted of collagen fibers which had lost their cross striation. The ultrastructure of the

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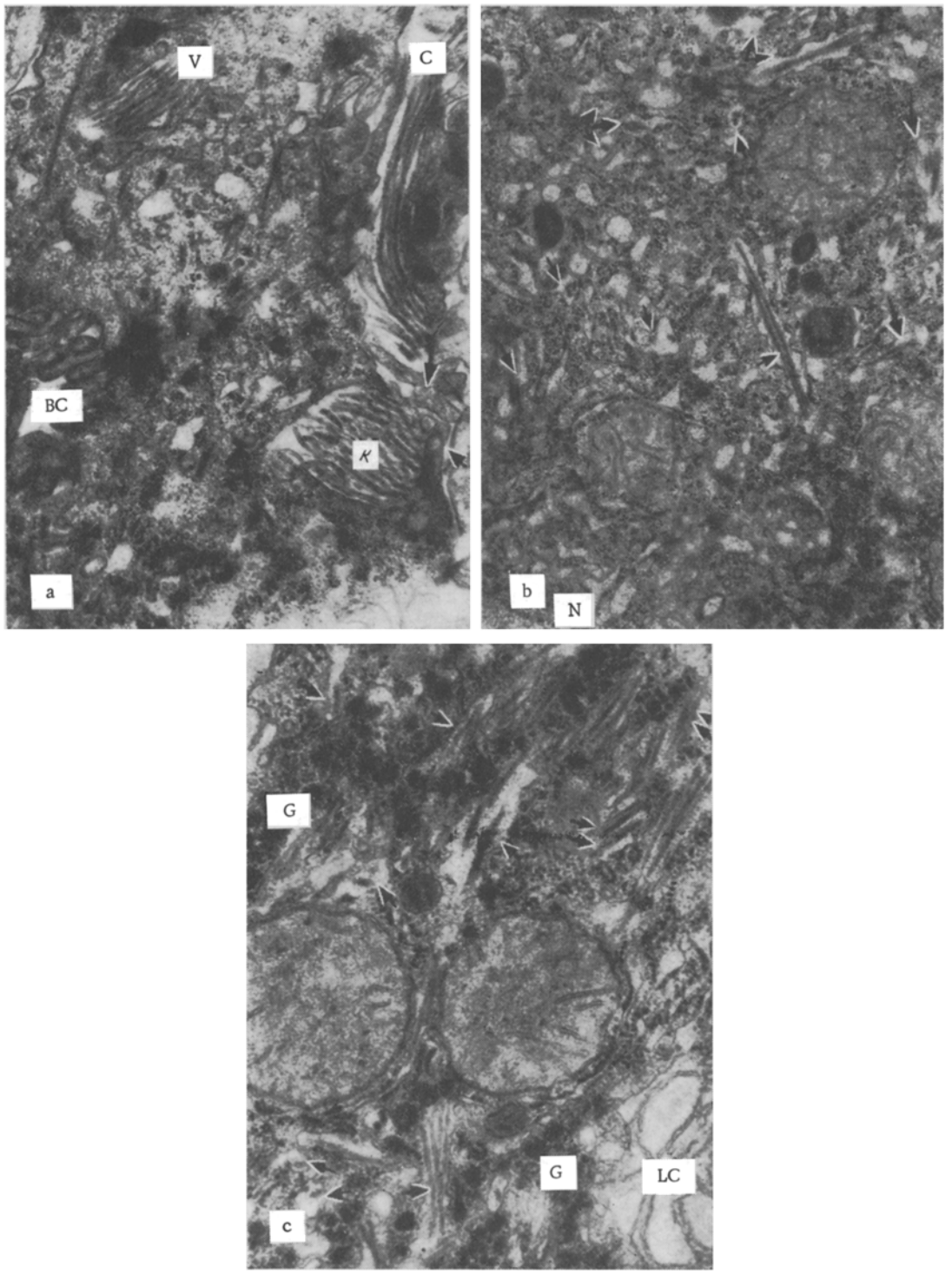

Fig. 1. Regeneration of cirrhotically changed mouse liver after partial resection: a) 10th day after resection: collagen uptake by hepatocyte (arrows). Vacuole with collagen can be seen in cytoplasm. C) Collagen, V) vacuole, BC) bile capillary, 40,000 ×; b) 15th day after partial hepatectomy: phagocytic vacuoles with collagen fibrils in cytoplasm of hepatocyte (arrows). N) Nucleus, 20,000 ×; c) 15th day after resection: multiple phagocytic vacuoles with longitudinally, transversely, and obliquely cut collagen fibrils in cytoplasm of hepatocyte (arrows). Characteristic cross striation of fibrils and fiber can be seen, around which the limiting membrane cannot be clearly identified (double arrows). LC) Lamellar complex; G) glycogen, 30,000 ×.

hepatocytes differed from that on the 5th day after resection in the presence of glycogen in their cytoplasm.

Just as in the resected material, 5 and 10 days after resection vacuoles containing single fibers or bundles of collagen fibers at different stages of lysis could be seen in some hepatocytes. Some of them were fragmented without cross striation. The number of hepatocytes containing intracellular collagen increased during regeneration of the organ. Whereas such hepatocytes were relatively infrequent in the resected material and 5 days after resection, their number increased 10 days after partial hepatectomy. Not one, but several vacuoles with disintegrating collagen could be found in some of these cells. Different stages of collagen uptake by hepatocytes also were observed (Fig. 1a). On the 15th day after resection a well-developed rough endoplasmic reticulum, hyperplasia and hypertrophy of the lamellar complex, numerous lysosomes and peroxisomes and also much glycogen could be observed in the hepatocytes. Consequently, most hepatocytes were actively functioning cells. Vacuoles with collagen fibrils, distributed diffusely throughout the cytoplasm, were found in many hepatocytes; in some cells the vacuoles were extremely numerous (Fig. 1b, c). Sometimes the limiting membrane of some of these vacuoles could not be clearly traced (Fig. 1c). In some preparations the number of hepatocytes containing disintegrating collagen in their cytoplasm at this time reached 30%. Such vacuoles were found in both "dark" and "pale" hepatocytes. No general rule could be discerned in the distribution of vacuoles with collagen in the cytoplasm of the hepatocytes.

The results indicate intensive phagocytosis of excess collagen by hepatocytes. This view is supported by the increase in the number of hepatocytes containing collagen in their cytoplasm during regeneration of the organ and the increase in the number of phagocytic vacuoles themselves, with disintegrating collagen in each cell.

During regression of cirrhosis of the liver a phenomenon of intracellular resorption of collagen by hepatocytes through phagocytosis is thus observed.

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