

SOME ULTRASTRUCTURAL ASPECTS OF REVERSIBILITY OF SCLEROTIC CHANGES IN THE LIVER

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The reversibility of cirrhosis of the liver has been studied mainly with the light microscope [5, 6, 14]. Ultrastructural aspects of this process have received much less study than histological and biochemical aspects [7-9, 15]. There have been only isolated electron-microscopic investigations of the reversibility of cirrhotic changes in the liver [1, 2, 10].

Since the most conspicuous morphological feature of regression of cirrhosis of the liver is a decrease in weight of the fibrous tissue, attention was concentrated in the present investigation on changes in ultrastructure of collagen and also on structural changes in the hepatocytes accompanying them.

EXPERIMENTAL METHOD

Cirrhosis of the liver was induced by subcutaneous injection of 0.2 ml of a 40% solution of CCl_4 in olive oil once a week for 5 months into noninbred male albino mice. To stimulate regeneration, the left lobe of the liver was resected in all animals 10 days after the last dose of CCl_4 . Material for investigation was taken during resection and 7 and 15 days thereafter. Material for histological study was fixed in 10% neutral formalin and stained with hematoxylin and eosin and by Van Gieson's method. Material for electron microscopy was fixed in glutaraldehyde, postfixed in OsO_4 , dehydrated, and embedded in Epon. Ultrathin sections were examined in the EMV-100L electron microscopes.

EXPERIMENTAL RESULTS

Examination of histological sections from pieces of liver taken during resection revealed marked annular cirrhosis with pseudolobule formation and considerable infiltration of

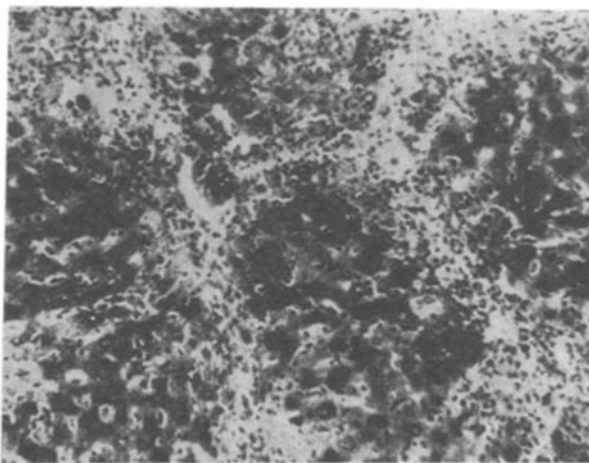


Fig. 1. Cirrhosis of the liver. Many lymphoid cells can be seen in the fibrous bands. Hematoxylin and eosin, 100 \times .

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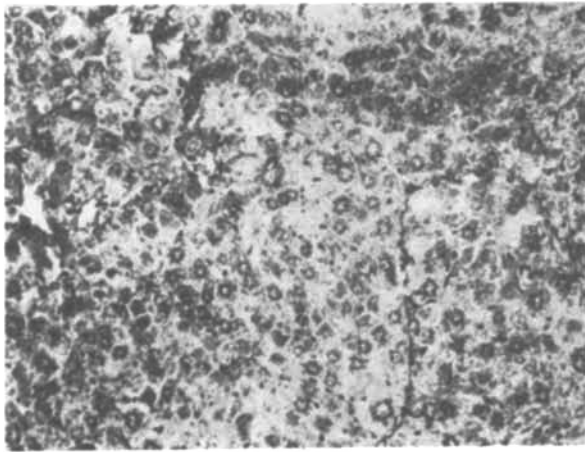


Fig. 2

Fig. 2. Liver 15 days after resection. Fibrous bands are much thinner, infiltration with lymphocytes is disappearing. Van Gieson, 100 \times .

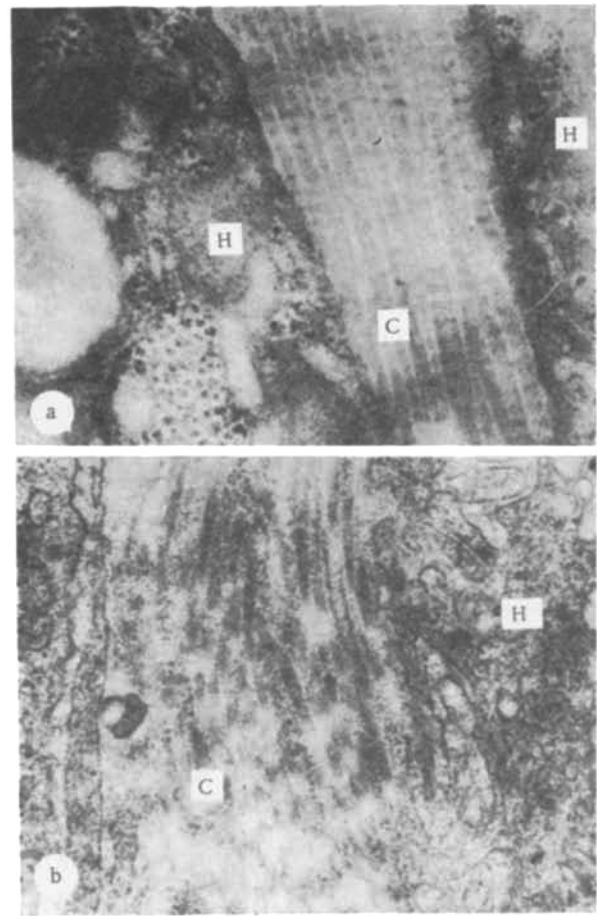


Fig. 3

Fig. 3. Resected material. a) Fibrous band consisting of mature, densely packed collagen fibers. C) Collagen, H) hepatocytes. 20,000 \times . b) 7 Days after resection. Disintegration of collagen fibers (C). H) Hepatocyte, 20,000 \times .

lymphocytes in bands of fibrous tissue (Fig. 1). The fibrous bands were much thinner 15 days after resection and infiltration gradually disappeared (Fig. 2).

Electron-microscopic investigation of the resected material revealed powerful bundles of mature collagen fibers among the hepatocytes and in Disse's spaces (Fig. 3a). Lymphocytes, polymorphonuclear leukocytes, macrophages, fibroblasts, plasma cells, eosinophils, and Ito's cells were found in Disse's spaces. The hepatocytes contained many lipid inclusions.

During regeneration of the liver the ultrastructure of the fibrous bands underwent considerable changes. The collagen fibers underwent disintegration, they stained more palely (loss of contrast), became thinner, and lost their characteristic cross-striation. Collagen bundles became looser in structure and floccular or finely granular masses appeared in them and gradually increased in number, due to progressive destruction of the collagen fibers (Fig. 3b). Transverse fragmentation of collagen fibers, which Perez-Tamayo also found during resorption of collagen in a carrageenin granuloma [11], was observed in the present investigation 7 days after resection.

The most characteristic changes in the hepatocytes during regression of cirrhosis were widening of the cisterns of the rough endoplasmic reticulum, the formation of numerous microvilli on the sinusoidal surface of the cells, and an increase in the number of lysosomes. These structural features are characteristic of cells with increased endocytotic activity and breaking down the ingested material with the aid of lysosomal enzymes. As the writer showed previously, collagen is the material phagocytosed by hepatocytes under the conditions described above [3, 4].

Extracellular fragmentation and resorption of collagen described above are evidently initiated by collagenase [12, 13], but later take place under the influence of lysosomal enzymes secreted by hepatocytes into the extracellular space. However, the second part of this hypothesis requires experimental verification *in vivo*.

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