MECHANISMS OF COLLAGEN RESORPTION IN CIRRHOSIS OF THE LIVER

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UDC 616.36-004-092

KEY WORDS: cirrhosis of the liver; hepatocytes; collagen.

The possibility of resorption of sclerotic tissue in the liver was first demonstrated in principle by Cameron and Karunaratne [4]. The regression of advanced sclerosis of the liver, previously considered irreversible, was next demonstrated [2], but the mechanism of this process has not yet been elucidated. Extracellular breakdown of collagen *in vitro* through the action of collagenase, which is found in sclerotically changed rat liver [9], has been shown. These findings have subsequently been developed in a number of investigations [7, 8]. Soviet investigators have made an electron-microscopic study of collagen resorption in the liver *in vivo* [1]. They observed swelling of collagen fibers, loss of their periodic striation, and conversion into homogeneous masses. The role of hepatocytes in reduction of the mass of fibrous tissue in the liver is not yet known.

This paper describes the results of an electron-microscopic study of the liver in cirrhosis and also during its regression.

EXPERIMENTAL METHOD

Noninbred male albino mice, in which cirrhosis of the liver was induced by subcutaneous injection of 0.2 ml of 40% solution of CCl_4 in olive oil once a week for 5 months, were used. So that the cirrhosis of the liver developing under the influence of chronic poisoning should undergo regression, the course of CCl_4 injection was stopped. In addition, 10 days after the last injection of CCl_4, the left lobe of the liver, was resected in all the animals. Many workers have found [3, 5, 6] that partial hepatectomy appreciably accelerates regeneration of the liver, and it was therefore hoped that under the conditions of this source regeneration of the organ, processes of resorption of excess fibrous tissue would be more clearly manifested. Material for investigation was taken during and 10 days after resection. For histological study the material was fixed in 10% formalin, for electron-microscopic study in OsO_4 or in glutaraldehyde, followed by postfixation in OsO_4, dehydration, and embedding in Epon. Ultrathin sections were examined in the ÉVM-100L electron microscope.

EXPERIMENTAL RESULTS

Bundles of collagen fibers could be seen in pieces of liver tissue removed at resection, in the Disse's spaces and between the hepatocytes (Fig. 1). Electron-microscopic examination revealed bundles of collagen of different thickness, and in most cases the fibers possessed cross-striation and were in close contact with the cell membrane of the hepatocytes. Lipid inclusions were present in the cytoplasm of the hepatocytes.

In nearly all the animals, individual fibers or bundles of collagen fibers were found in some hepatocytes, most frequently lying alongside the bands of collagen (Fig. 2). Not all the fibers detectable intracellularly contained cross-striations. Fragmented collagen fibers, which were losing or had already completely lost their striation and were converted into homogeneous masses, also were seen. Characteristic features of hepatocytes containing intracellular collagen were hyperplasia of the lamellar complex and an increase in the number of lysosomes compared with cells in whose cytoplasm no collagen was found. Lysosomes lay alongside intracellular collagen. Most frequently a vacuole containing collagen was "attacked" by several lysosomes. In such cases the electron density of these vacuoles increased considerably. Collagen in the hepatocytes was found throughout the cytoplasm, both at the biliary and at the vascular pole.

Central Research Laboratory, Kishinev Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 11, pp. 118-119, November, 1983. Original article submitted March 25, 1983.

 0007-4888/83/9611-1634$07.50

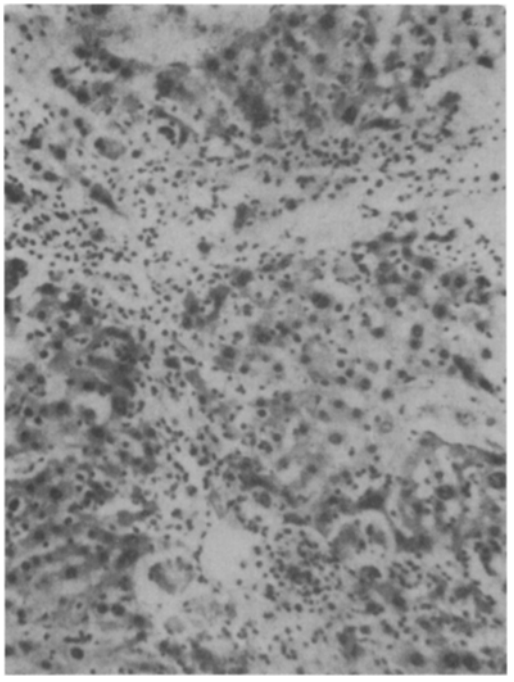

Fig. 1

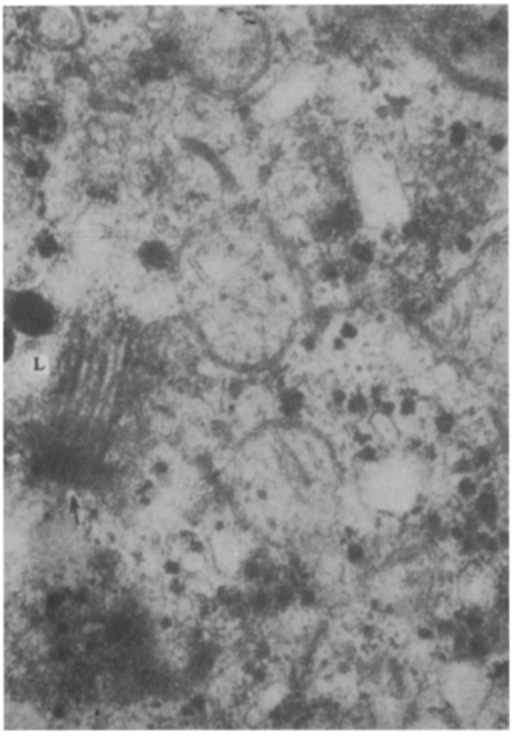

Fig. 2

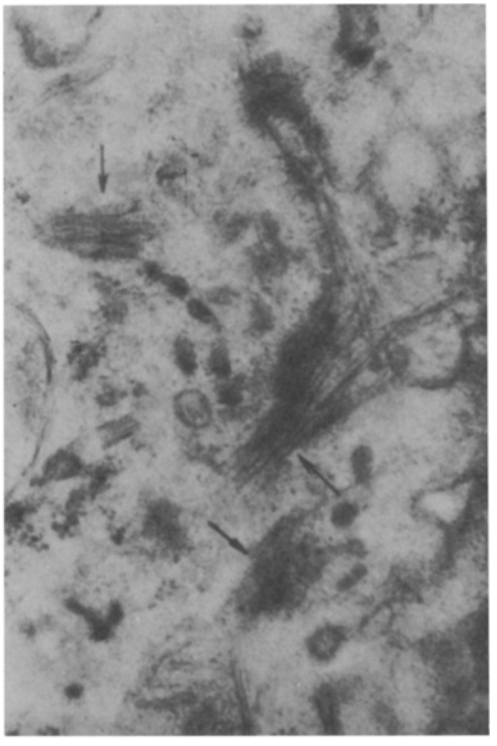

Fig. 3

Fig. 1. Mouse liver after injection of CCl_4 for 5 months: annular proliferation of connective tissue with pseudolobule formation. Hematoxylin and eosin, 100 ×.

Fig. 2. Area of cytoplasm of hepatocytes from resected material, in which groups of collagen fibers are clearly visible (arrows). 42,000 ×.

Fig. 3. Collagen fibers with characteristic cross striation in cytoplasm of hepatocytes 10 days after partial hepatectomy, with lysosomes (L) alongside. One lysosome has fused with the collagen (arrow). 30,000 ×.

Some of the bands 10 days after resection consisted of collagen fibers which were losing or had lost their cross striation. Glycogen was found in the cytoplasm of the hepatocytes. Just as in the resected material, collagen fibers were found in the hepatocytes (Fig. 3). Considering the overwhelming trend of the process (restoration of the parenchyma and resorption of fibrous tissue), and also the constant contiguity and fusion of the intracellular collagen with lysosomes, it can be postulated that the hepatocytes ingest excess collagen by phagocytosis and dissolve it with the aid of their lysosomal apparatus. Some of the collagen lysis products are evidently discharged from the hepatocytes into the bile, some enters the blood stream, and some is utilized by the hepatocytes for structural purposes.

No significant difference in phagocytic activity of the hepatocytes could be found at the moment of resection or 10 sec thereafter.

During regression of cirrhosis of the liver, vacuoles containing clearly formed or half-destroyed collagen fibers or bundles of fibers are thus found in some hepatocytes. Fusion of lysosomes with these vacuoles indicates that this phenomenon can be regarded as resorption of the excess collagen by phagocytosis.

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