diapedetic hemorrhages in the adjacent alveolar parenchyma, and only after exposure to US for 30 sec/cm^2 did a serous effusion on the pleura develop.

Endothoracic application of low-frequency ultrasound for therapeutic purposes must therefore have limited exposure: not more than 20 sec/cm^2. Contact of the wave guide with the tissue of the lung and pleura is unacceptable.

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SCLEROTIC CHANGES IN THE LIVER IN EXPERIMENTAL CHOLESTASIS AND THEIR REVERSIBILITY AFTER RE-ESTABLISHMENT OF BILIARY DRAINAGE

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The problem of reversibility of pathological changes in organs, and in particular, of sclerotic changes in the liver is of considerable urgency.

In the case of complete occlusion of the common bile duct in rats cirrhosis of the liver develops after 20 days, and progressive cirrhosis with ascites after 25-28 days [6]. This model of cirrhosis of the liver in rats can be obtained within a much shorter time than by the use of hepatotropic agents. Investigation of the reversibility of these cirrhotic changes in the liver after restoration of bile drainage into the intestine is of great theoretical and practical interest, but there is as yet no adequate experimental model with which to study this problem.

To investigate the morphogenesis of the sclerotic changes in the liver and their reversibility, the writers have created an experimental model of long-term cholestasis in rats followed by restoration of the outflow of bile into the intestine.

EXPERIMENTAL METHOD

An experimental model of mechanical jaundice was produced in 54 rats weighing 140-160 g by ligation of the common bile duct and its division between two ligatures. In order to observe the time course of the morphological changes, some rats (n = 24) with a ligated bile duct were killed after 5, 10, 20, and 30 days of cholestasis. The drainage of bile was restored in the remaining rats (n = 30) after cholestasis for 10 and 20 days. At these times the stumps of the duct were considerably dilated and contained transparent bile. Choledochoduodenostomy was performed by gluing the dilated duct to the duodenum. To restore the drainage of bile into the intestine, the bile duct was punctured through the duodenal wall, and the

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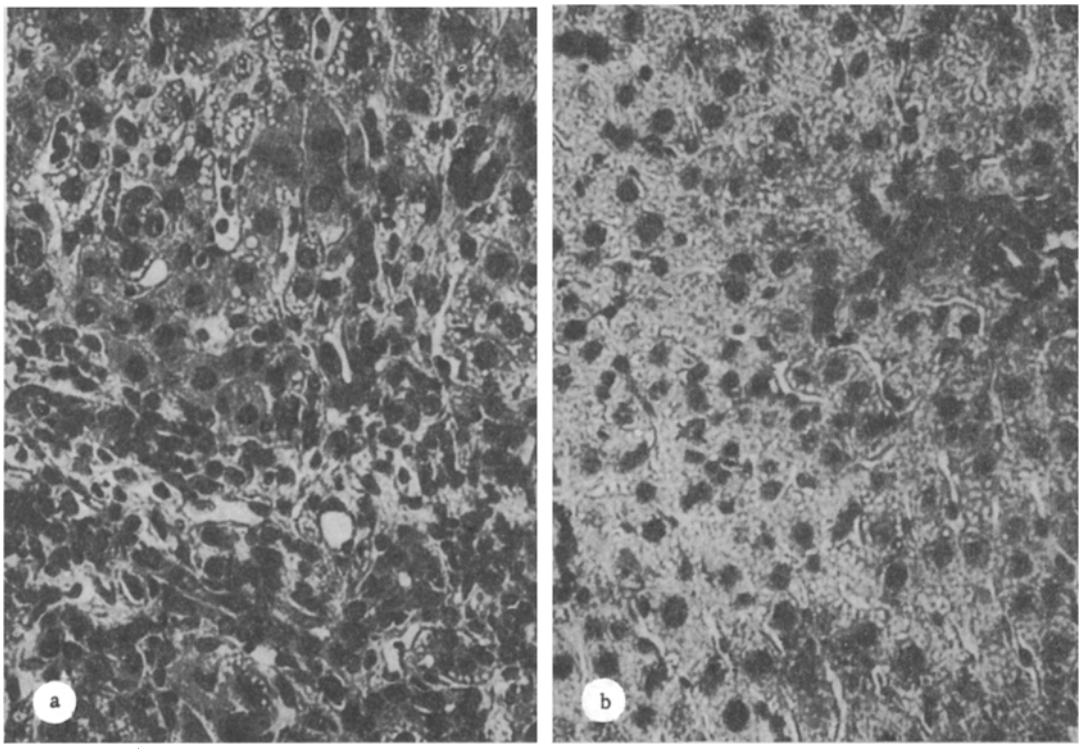

Fig. 1. Changes in structure of rat liver: a) Cholestasis for 10 days: loosening of structure and spreading of interlobular connective tissue along periphery of lobules, degeneration of liver cells (perilobular fibrosis of the liver); b) 1 month after resotration of biliary drainage. Hematoxylin and eosin, 180 ×.

site of puncture on the outer wall of the duodenum was sutured by means of atraumatic needles. Restoration of the outflow of bile into the duodenum was monitored by observing the animal's general condition, the bile-stained appearance of the urine, and the serum bilirubin level.

The time course of repair processes was studied in two series of experiments 15 and 30 days after choledochoduodenostomy.

Pieces of liver tissue were fixed in Carnoy's mixture of acetic-alcohol-formalin and embedded in paraffin wax; sections were stained with hematoxylin and eosin, by Mallory's and Gomori's methods, and with Schiff's reagent.

EXPERIMENTAL RESULTS

The morphological picture of the liver in animals on the 10th day of cholestasis revealed diffuse proliferation of connective tissue between the lobules in the form of fibrous septa, resembling perilobular fibrosis. At the periphery of the lobules connective-tissue cells partially compressed and disorganized the boundary layers of liver tissue. The proliferating interlobular connective tissue was edematous, loose in texture, and diffusely infiltrated by lymphocytes and histiocytes. The bile ducts had proliferated, their lumen was widened, and their epithelium flattened.

The majority of liver cells in the lobules were in a state of cloudy-swelling and vacuolar degeneration, and some of them in a state of necrosis. The biliary tubules were greatly dilated in some places. At the same time, large hepatocytes with hyperchromic nuclei and nucleolus were seen (Fig. 1a).

Fifteen days after restoration of biliary drainage the fibrous septa were reduced in thickness and the degenerative changes in the parenchyma had diminished. After 1 month of restoration of biliary drainage the degenerative changes had completely disappeared, and the interlobular connective tissue was reduced in thickness, although preserved in the portal triangular zones and was moderately infiltrated with cells. The structure of the bile ducts, blood vessels, and sinusoidal capillaries was completely restored to normal (Fig. 1b).

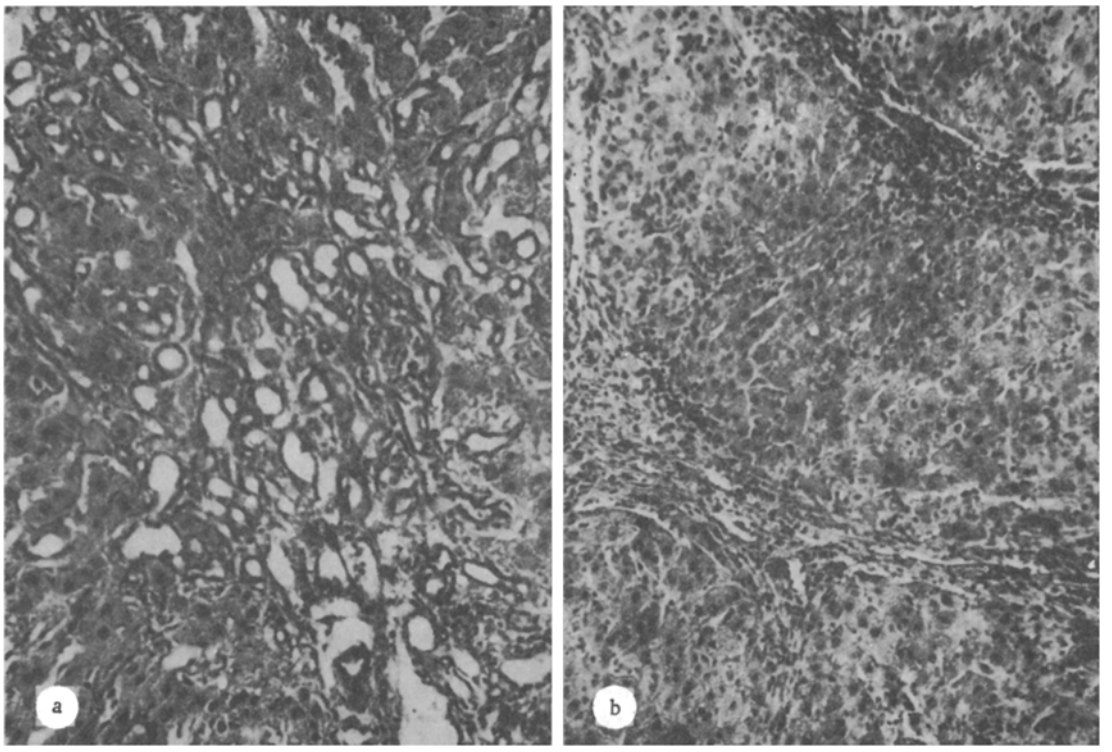

Fig. 2. Changes in rat liver tissue: a) Cholestasis for 20 days, intensive proliferation of connective tissue, marked proliferation of bile ducts, degeneration of liver cells (established biliary cirrhosis of the liver); b) 1 month after restoration of biliary drainage: liver lobules surrounded by bands of sclerotic tissue. Hematoxylin and eosin.

On the 20th day of obstructive jaundice established biliary cirrhosis of the liver was found with disturbance of the architectonics of both the parenchyma and stroma of the liver. The liver lobules were broken up by wide fibrous septa, with the formation of pseudolobules of various sizes. The extensive, loosely woven, edematous bands of interlobular connective tissue contained numerous proliferating bile ducts, with a greatly dilated lumen, and with flattened epithelial cells. Connective tissue fibers were concentrically arranged around these ducts, forming periductular fibrosis. Coarse bundles of collagen fibers along the course of the sinusoidal capillaries penetrated deeply within the lobules, dividing the hepatic laminae and forming pseudolobules and isolating the individual laminae, or sometimes even individual hepatocytes (Fig. 2a). The proliferating connective tissue was diffusely infiltrated by fibroblasts, macrophages, lymphocytes, and other cells. In areas of the parenchyma where the laminar structure of the liver was still preserved, the liver cells were in a state of cloudy-swelling and vacuolar degeneration, and some of them in a state of destruction. Meanwhile some hepatocytes were hypertrophied and intensely stained with oxyphilic dyes, and they contained a large nucleus and several nucleoli. Marked proliferation of the endotheliocytes and stellate cells of the sinusoidal capillaries was seen.

In this series of experiments repair processes were more marked after 1 month in the parenchyma of the liver and less marked in the stroma. The interlobular connective tissue remained around the whole perimeter of the lobule, in the form of wide or narrow septa, forming the boundaries of the lobules. Compared with that in the period of cholestasis, this tissue was rather denser and was moderately, and in some place densely, infiltrated with cells. The infiltrating cells included macrophages, mast cells, fibroblasts, plasma cells, lymphocytes, and fibrocytes. The number of bile ducts was considerably reduced, and some of them were in a state of destruction. Most hepatocytes were large, with one or two large nuclei. The sinusoidal capillaries were moderately dilated and the endotheliocytes and stellate Kupffer cells were unchanged (Fig. 2b).

Analysis of the results shows that the severity of the sclerotic changes was directly dependent on the duration of occlusion of the common bile duct. Disturbance of the outflow of bile into the duodenum for 10 days in rats led to the development of perilobular fibrosis of

the liver, separating the parenchyma into roughly equal areas. Development of fibrosis of the liver is observed in patients with obstructive jaundice, with chronic hepatitis, and other diseases of the liver [1, 5, 11]. The time course of repair processes after 10 days of cholestasis reveals gradual reduction of the excessively proliferating fibrous tissue and its complete resorption 1 month after removal of the cause of the pathological process. The principal role in complete resorption of the connective tissue is played not only by hyperplasia of the parenchymatous cells, but also by macrophages and fibroblasts located in the connective tissue [7, 9]. However, the intimate cellular mechanisms of resorption, on which the progressive decrease in the quantity of fibrous tissue is based, remain unexplained.

Sclerotic changes were manifested not only as thickening of the stroma and widespread infiltration of lymphocytes and histiocytes into the depth of the lobule, but also by the formation of connective tissue within the lobules, independently of the portal zones. The formation of collagen fibers within the lobules is found in patients with longstanding obstructive jaundice and chronic hepatitis [2, 4, 12]. Connective tissue cells formed inside the lobules pinch off groups of hepatocytes or single cells, thereby disturbing the exchange of materials between cells and blood.

Meanwhile besides degeneratively changed hepatocytes, hypertrophied hyperchromic hepatocytes also appear in the parenchyma, evidence of the marked powers of regeneration of the parenchyma, [3, 10]. In established cirrhosis of the liver removal of cholestasis nevertheless affected the course of the pathological process. Whatever the case, the sclerotic changes in the tissue did not progress further. The residual connective tissue after 1 month was condensed and separated from the neighboring hepatic laminae and moderately infiltrated by lymphocytes and histiocytes. Essential factors in normalization of the parenchyma were disappearance of the connective tisuse bands within the lobules and restoration of the normal structure of the sinusoidal capillaries of the liver, which is of great importance for normal functioning of the liver cells, and also for exchange of materials between these cells and the blood. Regression of cirhosis of the liver takes place much more slowly, with the result that the structure of the liver 1 month after restoration of biliary drainage still remained disturbed. Complete restoration of the normal structure of the liver evidently requires a long time [8].

The experimental model of obstructive jaundice can thus be used as an adequate model for the rapid production of cirrhosis of the liver, and the use of the Soviet MK-7 medical glue for restoring biliary drinage into the intestine enables the reversibility of the pathological changes in the liver to be investigated.

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