

# REGENERATION OF THE LIVER IN EXPERIMENTAL CIRRHOSIS AFTER LIGATION OF BRANCHES OF THE PORTAL VEIN

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In experimental cirrhosis of the liver produced by administration of  $\text{CCl}_4$  after ligation of a branch of the portal vein, lobes deprived of their blood supply rapidly diminished in size but complete death of the tissue did not take place. By the end of the third month, moderate regeneration had taken place. The intact lobes increased in size during the first week, to reach their size in healthy animals by the end of the third month. At the same time the histological structure of the intact lobes was almost completely restored to normal, fatty infiltration of the parenchyma had disappeared, and the glycogen content and succinate dehydrogenase activity showed a sharp increase.

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The work of Soviet and other investigators, clinicians, and morphologists had demonstrated the stimulating effect of various surgical and therapeutic procedures (partial hepatectomy, ligation of the bile ducts, arterialization of the portal blood, transumbilical administration of drugs) on regeneration of the cirrhotic liver [1-15, 17, 19]. Individual reports have indicated the effectiveness of ligation of branches of the portal vein in this condition [16, 18, 20]. The most complete study of this problem has been undertaken by Cerny [16]. However, he has given only a very limited description of the pathohistological changes in the liver, especially the histological structure of the lobes from which the portal blood flow was excluded.

The object of the present investigation was to make a macroscopic and microscopic study of reversibility of cirrhosis of the liver after ligation of branches of the portal vein.

## EXPERIMENTAL METHOD

Experiments were carried out on 35 male albino rats weighing 150-225 g (five of these animals in which the vessel was not ligated acted as controls). Twice a week for 5 months the experimental rats received 0.2 ml of a 50% solution of  $\text{CCl}_4$  per 100 g body weight through a gastric tube. After production of cirrhosis of the liver, laparotomy was performed under superficial ether anesthesia and the left trunk of the portal vein was ligated. The rats withstood the operation well.

The animals were sacrificed in groups of 3-5 rats at a time by decapitation 24 and 72 h, 7 and 14 days, and 1 and 3 months after the operation. Small pieces of liver were fixed in 10% neutral formalin and in Carnoy's fluid, and frozen sections were made. The sections were stained with hematoxylin and eosin and by Van Gieson's method, lipids were detected with Sudan III, glycogen by Shabadash's method, and succinate dehydrogenase by Nachlas's method using nitro-BT.

## EXPERIMENTAL RESULTS

After ligation of the left trunk of the portal vein, lobes of the liver deprived of their portal blood flow diminished rapidly in size on macroscopic examination, and became paler than in the control, especially

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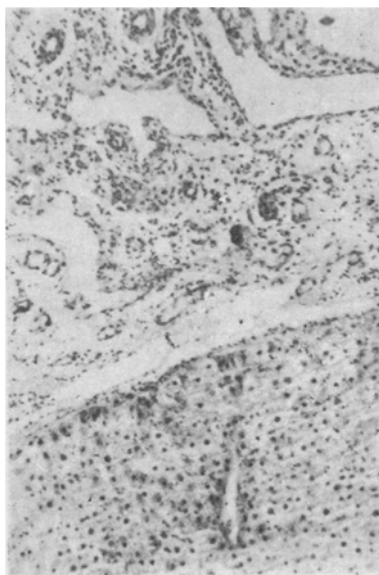


Fig. 1. Formation of vessels of arterial type in the liver capsule 1 month after ligation of the left branch of the portal vein. Hema-toxylin-eosin, 120 $\times$ .

during the first 2 weeks. By the end of the third month of observa-tion their surface had become rather smoother, and showed a red-dish coloration against the general yellowish brown background.

On microscopic examination during the first week after liga-tion of the vessel, besides evidence of annular cirrhosis of the liver considerable dilatation of the eccentrically disposed central veins could be observed, one such vessel occurring every 10-15 pseudo-lobules. Branches of the portal vein in the triads were considerably collapsed, with swollen endothelial cells sometimes occupying the lumen. Besides a combined histiocytic and lymphocytic reaction, deposition of hemosiderin could be seen in the interlobular connec-tive-tissue septa.

Frequently areas of necrosis of liver tissue and degeneration of hepatocytes, showing as moderate fatty infiltrations of the cyto-plasma, were observed, glycogen was almost completely absent, and succinate dehydrogenase activity was very low. Few binuclear cells were present, and by the end of the second week mitotic figures were frequently observed.

One month after the beginning of the experiment numerous newly formed vessels of arterial type were observed in the moder-ately thickened capsule of the liver and in the interlobular connec-tive-tissue septa (Fig. 1). The parenchyma of the organ became more congested on account of an increase in the circulation of blood

through numerous small vessels located in the connective-tissue septa between the pseudolobules. Veins in the triads were increased in diameter and surrounded by small arteries. Ill-defined necrobiotic changes were observed in the hepatocytes, their cytoplasm was slightly infiltrated with fat, numerous binuclear cells were seen, mitotic figures were more frequent, and the deposition of glycogen was not so strictly regular: in places it was abundant, and elsewhere present in small quantities; an increase in succinate dehydrogenase activity was observed.

Ninety days after ligation of branches of the portal vein, annular cirrhosis was still present in the lobes of the liver deprived of their blood supply, but the interlobular connective-tissue septa were consid-erably thinner, their infiltration with round cells was reduced, newly formed arterial vessels were more numerous, and frequently the small pseudolobules merged to form larger lobules (as a result of absorption of collagen), and the cushion-like protrusions of the subcapsular zones were partially obliterated. Fre-quently very large (twice the control size or more) hepatocytes, sometimes with high mitotic activity, were frequently seen in these protrusions. The glycogen content in the parenchymatous cells of the lobes and the succinate dehydrogenase activity were increased.

After division of the left trunk of the portal vein, lobes of the liver with an intact portal circulation were increased in volume on macroscopic examination by the end of the first week of observation, and after 14 days their surface was covered with medium-sized nodules instead of small, and was somewhat smoother than normally; the tissue was brownish red in color. By the end of the third month after ligation of the vessel they were enlarged to three times the control size or more, and the nodularity of the surface was less pronounced still.

On microscopic examination during the first 3 days after ligation of the vessel, against the back-ground or marked degenerative changes in the hepatocytes of the intact lobes of the cirrhotic liver there was considerable infiltration of the interlobular connective tissue, mainly by round cells, and foci of ne-crosis were frequently observed. Parenchymatous cells, twice or three times larger than in the control, with very large, sometimes hyperchromic nuclei and with high mitotic activity, were found in the central and middle parts of the lobules. The borders of many cells were indistinguishable. The tissue was con-gested and the central veins dilated. Fat, in the form of small and medium-sized droplets, filled the cyto-plasm, where only small amounts of glycogen were present. The glycogen content in the large hepatocytes was considerably increased. Succinate dehydrogenase activity was relatively high.

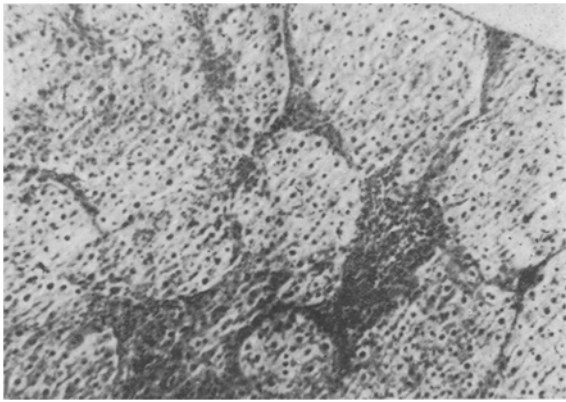


Fig. 2. Thinning and disappearance of interlobular connective-tissue septa in intact lobes of the liver 1 month after ligation of the vessel. Hematoxylin-eosin, 120 $\times$ .

One week after the operation the zones of regeneration occupied a larger area than initially. Hepatocytes 3 or 4 times the control size, with hyperchromic nuclei and high mitotic activity, were visible here. Fatty infiltration of the cytoplasm was not progressive in character, and the glycogen content and succinate dehydrogenase activity were considerably increased.

Smoothing of the surface of the intact lobes, thinning of the interlobular connective-tissue septa, the formation of new arterial vessels of the shunting type, and marked dystonia of the central veins were observed after 14 days. Frequently situated close to the triads, they formed anastomoses with interlobular branches of the portal vein. Bile ducts became numerous, and many of them were lengthened and stretched. The foci of regeneration occupied considerable areas, but no tendency toward an increase in their activity could be found. Large quantities of fat were detected

in the cytoplasm of the parenchymatous cells, while the glycogen content and succinate dehydrogenase activity were higher than at the preceding periods of observation.

One month after ligation of the vessel, considerable thinning of the previously thickened capsule and interlobular connective-tissue septa, amounting sometimes to their total disappearance (Fig. 2) on account of absorption of collagen, was observed. The normal liver structure was generally restored: the hepatocytes were of the usual size and arranged radially. The number of central veins was increased, and shunts between them and branches of the portal vein were more frequent. Fatty infiltration of the parenchymatous cells was not found, the glycogen content was very high in the pseudolobules with a relatively normal histological structure, and succinate dehydrogenase activity there was also very high.

Ninety days after the operation the general structure of the lobules of the cirrhotic liver with an intact portal blood flow was close to normal. However, some areas were found in which the processes of regeneration continued. The lumen of the central veins remained dilated. In the interlobular connective-tissue septa numerous newly formed arterial vessels of small caliber could be seen.

Hence, in experimental cirrhosis of the liver produced in rats after ligation of the left branch of the portal vein, during the first week there was a rapid decrease in size of the lobes from which the portal blood flow had been excluded, but the necrobiotic processes in these lobes were ill-defined and complete death of the tissue did not take place.

One month after the beginning of the observations, numerous newly formed vessels of arterial type could be observed in the capsule and interlobular connective-tissue septa. These vessels improved the blood supply of the organ and maintained its viability by the collateral circulation. By the end of the first month and in particular in the third month of the experiment, progressive regenerative processes were found in lobes from which the circulation had been excluded.

In lobes of the liver with an intact portal blood flow, marked regenerative processes were found in the first week after ligation of the vessel, against the background of degenerative, necrotic, and inflammatory changes. These regenerative processes, which were found initially in the central and intermediate parts of the lobules, subsequently extended to the peripheral zones.

After the fourteenth day of observation the regenerative changes in the liver continued to progress, but by the end of the first month after the operation they had subsided, although they did not completely disappear even by the end of the experiment (3 months). This led to a marked increase in the size of the intact lobes of the organ (to the size observed in healthy rats), and to the almost complete restoration of their normal histological structure. This picture was accompanied by absence of fatty infiltration of the parenchymatous cells, very considerable accumulation of glycogen, and high succinate dehydrogenase activity.

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