ANATOMICAL CHANGES IN THE LIVERS OF DOGS FOLLOWING MECHANICAL CONSTRICTION OF THE HEPATIC VEINS *

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This paper is a report of the changes observed in the livers of seventeen dogs whose hepatic veins were mechanically constricted for periods of 7 to 30 minutes for the purpose of studying the chemistry in the blood during the succeeding 24 to 72 hours. Practically all of the recorded anatomical studies of the liver following alterations in the hepatic circulation have been based upon permanent changes in the blood flow and, therefore, are concerned with more or less chronic modifications of that organ. Thus, the results of ligation of the hepatic artery have been investigated by Holst,[1] Behrend, Radasch and Kershner,[2] Ritter,[3] Hori,[4] Loeffler,[5] and others. Bainbridge and Leathes,[6] de Josselin de Jong,[7] Rous and Larimore,[8] Papilian,[9] Chiari,[10] and others, have studied the effect upon the liver of either ligation or thrombosis of the portal vein. Zimmerman and Hillsman [11] placed metal rings about the vena cava between the entrance of the hepatic veins and the heart. Hess,[12] in 1905, and more recently Satke [13] and Saborowsky [14] have reviewed the literature and discussed the results of obliterating endophlebitis of the hepatic veins. There are also occasional reports in the literature of alleged retrograde embolism of the hepatic veins (Heller,[15] Risel,[16] Meixner,[17] and Reiniger [18]). But in all of the above experiments and observations the alteration in the hepatic circulation was continuous. We have been unable to find any studies of the changes in the liver resulting from a sudden and complete, but temporary, closure of the hepatic veins.

Mechanical constriction of the hepatic veins by the method described by Simonds and Brandes [19] causes an immediate increase in the size of the liver, which becomes enormously distended with blood and dark brownish purple in color. This condition continues until

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the obstruction is released, when the liver promptly becomes smaller and somewhat paler. This procedure deprives the liver cells of oxygen, subjects them to a considerable increase in pressure, interferes with their nutrition and permits the accumulation of metabolic products in the surrounding medium during the period of constriction.

Of the seventeen dogs used in these experiments, one died 4 hours after the operation in typical hypoglycemic convulsions, two were sacrificed after 24 hours, eleven after 48 hours, two after 72 hours, and one after 7 days.

The liver weight-body weight ratio in these animals was distinctly increased, the mean being 0.0376 ± 0.0035, the individual ratios ranging from 0.025 to 0.047, only two being normal or below. Junkersdorf [20] found the liver weight-body weight ratio in normal dogs to be 0.030; Simonds and Brandes [21] obtained a mean ratio of 0.0303 in thirty-one normal dogs. The mean ratio in these animals was, therefore, approximately 25 per cent higher than the normal.

The increase in the weight of the liver was due in part to edema. Simonds and Brandes [22] observed an average increase of 2.5 times the normal outflow from the thoracic duct during mechanical constriction of the hepatic veins. On the basis of the microscopic examination of livers immediately, and 24 hours after constriction, it is assumed that much of this excess flow of lymph comes from the liver. The most marked change is in the lymphatics which surround the sublobular veins, many of which are encircled by widely dilated lymphatics filled with hyaline coagulated material (Fig. 1). These are apparently the radicles of the lymph vessels which follow the hepatic veins to the inferior vena cava, and thence along this vessel through the diaphragm into the posterior mediastinum. The connective tissue about these veins was rendered loose-meshed by accumulation of fluid between the cells. This can probably be accounted for as a result of damage to, and subsequent thrombosis of, the larger lymph vessels about the main branches of the hepatic veins. As shown by Opie [23] trauma is often an etiological factor in lymphatic thrombosis. The periportal connective tissue was also edematous.

Another element, of less importance, in the increase in weight of the livers of these dogs is the irregularly distributed increase of

blood. During constriction the amount of blood within the liver is enormous, but upon releasing the constriction most of the accumulated blood promptly escapes and when examined after 24 to 72 hours the liver as a whole is relatively poor in blood, with only a few scattered areas in which the central veins and adjacent sinusoids are distended with red cells.

On microscopic examination with low power one of the most striking features is the relative paleness of the central portion of the lobules (Fig. 2). The hepatic cells are swollen, more or less granular, many contain round clear spaces or vacuoles and some are without nuclei (Fig. 3). The vacuoles do not stain with osmic acid. The visible nuclei in this portion of the lobule vary greatly; some are swollen, extremely pale and washed out; others are compact and pyknotic, and relatively few are normal. The markedly swollen condition of these cells narrows, and, in places, practically obliterates the sinusoids so that the central part of the lobules is almost bloodless. At the periphery of the lobules is a zone of varying width in which the liver cells are more nearly normal. From this it appears that the hepatic cells in the central one-half or two-thirds of the lobule are less resistant to injury than those in the peripheral portion. A similar differential distribution of cell damage has been observed in other conditions, *e.g.*, chloroform poisoning, chronic passive hyperemia, and so on. In these conditions either a toxic agent or a disturbance of the circulation in the liver acts over a more or less long period of time. It has been suggested that the greater damage to the centrally located cells in the liver lobule is a result of their greater distance from the fresher part of the blood supply, the peripheral cells having the first opportunity to secure oxygen and nutriment from the blood as it percolates through the lobule, while the central cells receive only blood which has been depleted of substances essential to their life. But in our experiments the entire circulation through the liver was stopped temporarily. Hence both central and peripheral hepatic cells were subjected to identical conditions. The differential distribution of evidences of cell damage described above in the livers of our animals indicates a greater actual susceptibility to injury on the part of the cells in the central part of the lobules as compared with those of the periphery. Mallory [24] has suggested that the greater vulnerability of the central cells of the liver lobules is due to their greater functional activity

and higher degree of specialization. The results of our experiments tend to confirm this view.

A variable number of central and sublobular veins are filled with clear structureless masses, some of which stain blue, others dark red (Fig. 4). As a rule, lobules whose central veins are thus occluded contain more blood than the adjacent lobules.

A characteristic finding in all of these animals is the presence of masses of cells within the sinusoids (Figs. 5 and 6). These cells are of three types: an occasional lymphocyte, a few polymorphonuclear leucocytes and a greater number of mononuclear cells with large round, oval or indented nuclei and moderately abundant cytoplasm. These latter cells appear to have originated from proliferation of sinusoidal endothelium. These cell masses are either small and compact and lie in an oval dilatation of the sinusoid, resembling those described by Simonds[25] and by Manwaring, French and Brill[26] in anaphylactic and peptone shock, or they are larger and more diffusely and loosely arranged in several adjacent sinusoids, but consist of the same cell types as the above. Within this second form of cell masses the cords of liver cells are disrupted and many of the included hepatic cells are swollen, stain with eosin and are without nuclei. These areas therefore have much in common with the focal necrosis described by Mallory[27] in typhoid fever.

Cell groups of the first type are most numerous in the dog that was allowed to live for 7 days and whose hepatic veins were constricted for 20 minutes. In many of these masses, especially in the 24 hour dogs, a red hyaline matrix is easily visible. These compact intrasinusoidal masses are probably of the same nature as those designated by Pearce[28] as conglutination thrombi. Their manner of formation is probably as follows. During the stagnation of the blood in the sinusoids, while the hepatic veins are constricted, a group of red cells becomes packed into a firm mass which cannot be broken up when the circulation is restored. These later fuse into a hyaline matrix in which is entangled an occasional lymphocyte and into which may wander a few polymorphonuclear leucocytes. The presence of this "foreign body" within the sinusoid stimulates the proliferation of the adjacent lining endothelium from which is derived the chief part of the cell content of the mass.

In the second type of cell mass there is no evidence of fusion of red cells. The presence of a group of necrotic hepatic cells may

serve to stimulate the proliferation of the sinusoidal endothelium. If this interpretation is correct, the process is the reverse of that described by Mallory [27] as the probable pathogenesis of focal necrosis in typhoid fever.

In all these animals the Kupffer cells contained an abundance of brown, granular pigment resembling hemosiderin.

Summary

The livers of dogs examined 24, 48 and 72 hours and 7 days after mechanical obstruction of the hepatic veins for periods of 7 to 30 minutes showed the following changes.

1. A mean increase of 25 per cent in the liver weight-body weight ratio, due to edema and to swelling of the hepatic cells.

2. Swelling, granulation, vacuolization and extensive necrosis of the hepatic cells in the central half or two-thirds of the liver lobules.

3. Marked dilatation of the perivascular lymphatics surrounding the sublobular veins.

4. The presence of hyaline thrombi in many central and sublobular veins.

5. Intrasinusoidal cell masses of two types: (1) small, compact, occluding masses probably originating in "conglutination thrombi" of red cells, and (2) larger, more diffuse and branching cell masses.

6. Hemosiderosis of Kupffer cells.

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DESCRIPTION OF PLATE

PLATE 28

FIG. 1. Distention of the perivascular lymphatics about a sublobular vein. × 100.

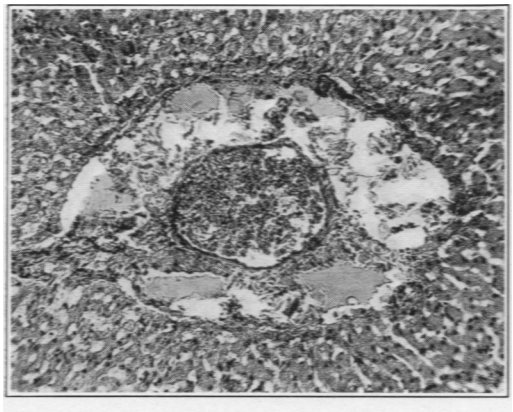
FIG. 2. Lower power field showing pale central portions of lobules. × 20.

FIG. 3. Swelling and necrosis of liver cells. × 325.

FIG. 4. Hyaline thrombus in central vein. × 200.

FIG. 5. Compact cell masses in sinusoids. × 160.

FIG. 6. More diffuse cell masses in sinusoids. × 200.



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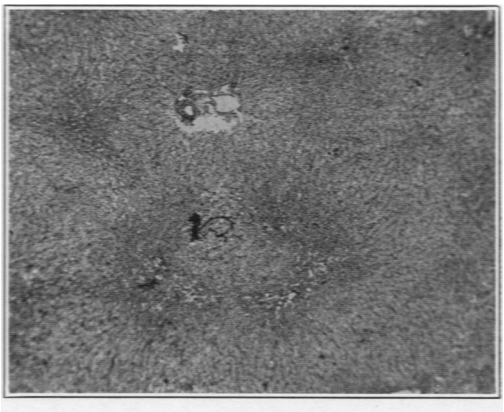

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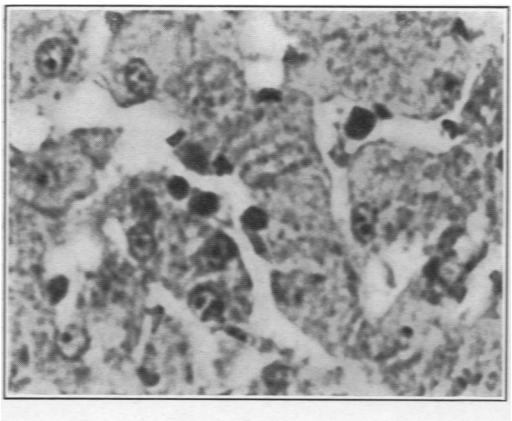

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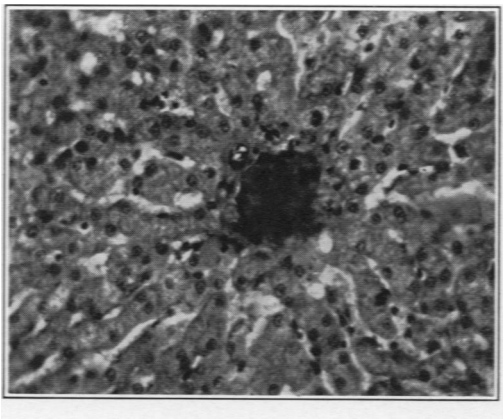

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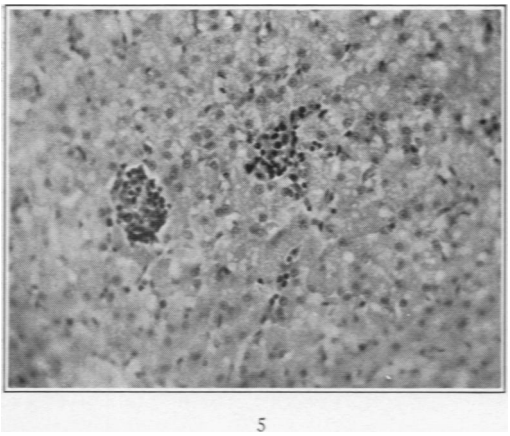

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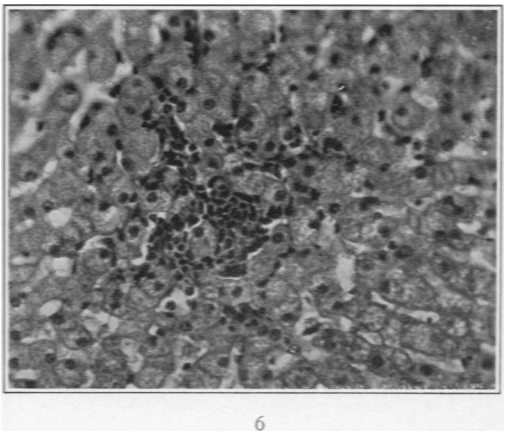

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