In experimental paraquat poisoning a definite parallel is thus observed between the biochemical and morphological changes in the tissues. It can be tentatively suggested that depression of SOD activity and the increase in the concentration of free radicals found in this condition are among the causes of development of proliferative processes manifested as a combination of characteristic pathological and morphological changes.

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EFFECT OF KUPFFER CELL BLOCKADE ON THE DEVELOPMENT OF ACUTE TOXIC HEPATITIS

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In previous investigations we showed that recovery of the mass of the liver after partial resection [3, 4] and injury and repair of the liver structure after administration of a single dose of a hepatotropic poison [2] depend on the functional state of the hepatic stroma and, in particular, of the Kupffer cells. Preliminary stimulation of the system of mononuclear phagocytes by the bacterial polysaccharide prodigiosan [1] was found to promote the more rapid regeneration of hepatocytes after partial resection of the liver, and the resistance of the hepatocytes to CCl_4 was increased. Conversely, preliminary loading of the Kupffer cells with colloidal iron carbonyl, with a strictly determined granule size, retarded repair of the liver after partial hepatectomy by inhibiting the rate of DNA synthesis in the hepatocytes and their mitotic division.

The object of this investigation was to study the course of acute toxic hepatitis in rats after blockade of the Kupffer cells.

EXPERIMENTAL METHOD

Wistar rats weighing 200-250 g were used. The animals in the experiment received an intravenous injection of 1 ml of 10% colloidal iron carbonyl-phosphate, grade R-100F, with a particle size of 0.8-1.5 μ, suspended in 5% starch in 0.85% NaCl solution. The control rats received 1 ml of starch solution. The animals of the experimental and control groups were given a subcutaneous injection of 0.2 ml of a 40% solution of CCl_4 in vegetable oil per 100 g body weight 2 h after the intravenous injection. Rats of the experimental and control groups were decapitated in batches of 4-6 at a time, 16, 24, 48, and 72 h later. The liver was fixed in Carnoy's mixture and embedded in paraffin wax. Sections were stained with hematoxylin-eosin and examined under the light microscope.

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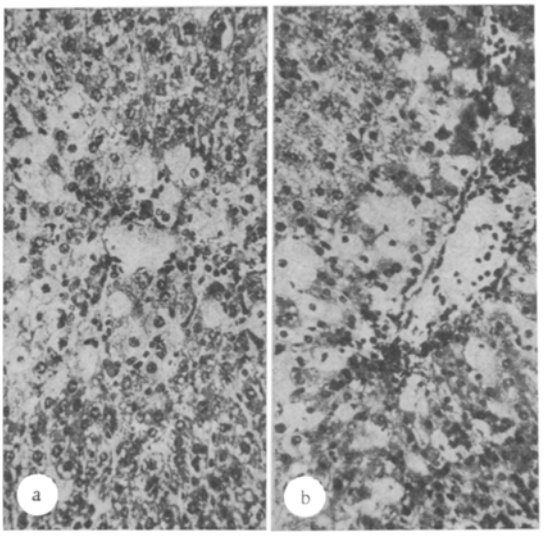

Fig. 1

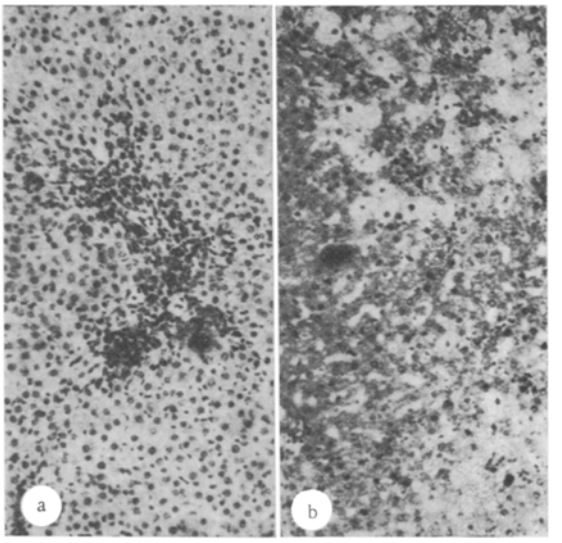

Fig. 2

Fig. 1. Section through rat liver. Typical variant of injury to hepatocytes 16 h after injection of CCl_4. a) Control: centrilobular necrosis of hepatocytes; b) experiment: necrosis of hepatocytes along course of portal tract. In both cases, staining with hematoxylin-eosin, 400×.

Fig. 2. Section through rat liver 48 h after injection of CCl_4. a) Control: intensive repair processes (160×); b) experiment: persistence of injury to hepatocytes (400×).

EXPERIMENTAL RESULTS

Clearly defined changes, namely destruction and lysis of the liver cells, with acidophilic and balloon degeneration, developed in the liver of the control rats 16 and 24 h after injection of CCl_4 (Fig. 1a). The size of the lesion was usually confined to the central zones of the hepatic lobule (zone III according to Rapoport). During the same periods, degenerative necrotic changes in the hepatocytes of similar character were observed in the experimental animals. However, unlike in the control, they were not confined to the centrilobular regions but partly affected the periportal areas also (Rapoport's zone I) (Fig. 1b). On the whole, after blockade of the Kupffer cells a tendency toward generalization of damage to the hepatocytes was noted.

After 48 h zones of necrosis of hepatocytes were virtually no longer detectable in the control, but foci of infiltration consisting of mononuclear cells with an admixture of polynuclear cells were localized in the center of the lobules (Fig. 2a). As a rule fatty infiltration of the hepatocytes was clearly visible. At the same time, large foci of necrosis of hepatocytes continued to appear in the experimental rats. In some cases necrotic areas were infiltrated with mononuclear cells, in others the foci of necrosis were unaccompanied by any reaction of the mesenchyme (Fig. 2b).

After 72 h the structure of the liver in the control series was fully restored, and only small foci of concentration of mononuclear cells along the course of the vessels remained as evidence of the previous injury. Meanwhile zones of necrosis and degeneration of hepatocytes, infiltrated with mesenchymal cells, continued to be discovered in the experimental series (Fig. 3).

The effects of CCl_4 are thus significantly modified if it is injected 2 h after loading of the hepatic reticuloendothelial system with an inert colloid. By the time of poisoning, iron granules were found in 2/3 to 4/5 of the total population of hepatic macrophages, but they were not found in the endothelial cells or, still less, in the hepatocytes. After 48 h and, in particular, after 72 h, numerous concentrations of cells loaded with iron were detected (Fig. 3), whereas along the course of the sinusoids were located Kupffer cells not containing iron granules. Consequently, blockade of the Kupffer cells persisted only during the first few hours after their loading with colloidal particles, and later, on the average after 2 days, depression was replaced by reactivation of the hepatic macrophage system. Other investigators reached the same conclusion [8, 9]. This fact must be taken into account when results reflecting different functional shifts after loading of the reticuloendothelial system with inert colloids are analyzed.

During Kupffer cell blockade in the present experiment the hepatotropic poison induced more generalized injury to the hepatocytes against the background of slowing of repair processes in the liver. By contrast, during

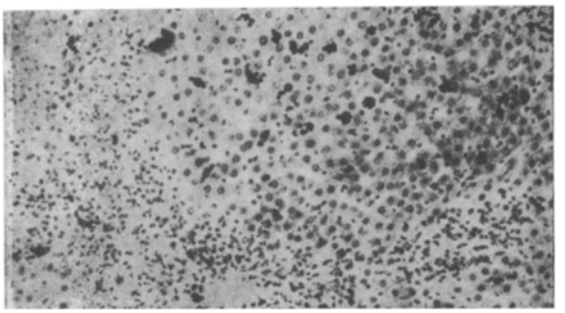

Fig. 3. Section through rat liver, 72 h after injection of CCl_4, experiment: extensive zones of destruction and infiltration; concentration of cells loaded with iron particles can be seen (160×).

activation of the Kupffer cells regeneration of the hepatocytes and restoration of the structure of the pathologically changed liver were accelerated [2, 4]. These results are in agreement with data showing the active participation of macrophages in regenerative processes and, in particular, in the healing of skin wounds [5, 7].

It can be concluded from our results that Kupffer cells play an important role in the pathogenesis of acute hepatitis. However, special investigations are needed to elucidate the mechanisms of the role of Kupffer cells in the development of liver diseases. The following suggestions appear most realistic at the present time. First, an activated liver macrophage may secrete a complex of factors potentiating regeneration of hepatocytes into the surrounding medium. In this connection it is interesting to note that repair processes in the liver in our experiments were appreciably activated during its repopulation by recent forms of macrophages. Second, the level of endotoxinemia depends on the functional state of the Kupffer cells, and endotoxins of the intestinal microflora potentiate the action of hepatotropic poisons [6].

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