tinguished to be regarded as cells in the resting state and in the synthetic and postsynthetic periods of the cell cycle respectively. Single large pale cells (Fig. 2a), containing few organelles, began to appear in the periportal zone 96 h after injury, and these could be regarded as relatively dedifferentiated cells [1] (Fig. 3b).

No destructive changes were found 120-168 h after administration of allyl alcohol. The number of cells giving a positive PAS reaction was increased, a sign of regeneration. The dark cells also were shifted into the intermediate region between the periportal and middle zones, and the number of pale cells in the periportal zone was increased. The massive appearance of pale cells in the periportal zone coincided in time with an increase in the number of cells in mitosis (Table 2), and this confirmed the hypothesis of dedifferentiation of these cells.

Degenerative changes, followed by proliferative changes after injury to the liver by allyl alcohol, have been described by other workers also [9, 11]. However, the intensity of the changes was weaker in the present experiment because of the small doses, and this had an effect on the localization and kinetics of regeneration [7].

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EFFECT OF HUMAN BLOOD SERUM AND CIRRHOTIC LIVER EXTRACT ON REGENERATION OF THE MOUSE LIVER AFTER PARTIAL HEPATECTOMY

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The study of the regulatory mechanisms of cell division is a fundamental problem in both biology and medicine. However, the mechanisms regulating mitotic activity of the hepatocytes in patients with cirrhosis of the liver have been inadequately studied, although their understanding is of great importance to the discovery of the pathogenesis of cirrhosis.

The writers showed previously that liver extract and blood serum from patients with active cirrhosis of the liver stimulates mitotic activity of hepatocytes in the mouse liver regenerating after partial hepatectomy [2].

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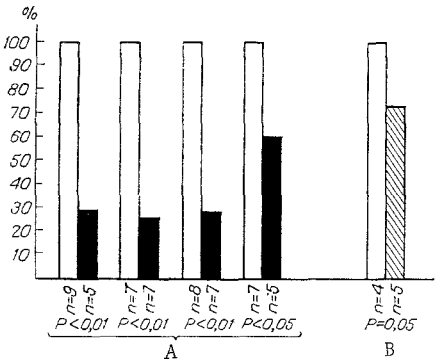

Fig. 1

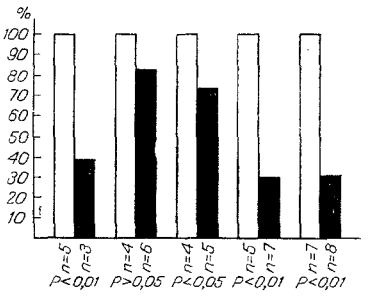

Fig. 2

Fig. 1. Effect of blood serum (A) and liver extract (B) of patients with inactive cirrhosis on mitotic activity of regenerating mouse liver. Ordinate, mitotic index, in % of control (unshaded columns), taken as 100%. n) Number of mice.

Fig. 2. Effect of blood serum of patients with active chronic hepatitis on mitotic activity of regenerating mouse liver. Legend as in Fig. 1.

To analyze the mechanisms of this phenomenon, in the present investigation the effect of blood serum and liver extract from patients with inactive cirrhosis of the liver and with active chronic hepatitis on mitotic activity of the regenerating liver was studied.

EXPERIMENTAL METHOD

Blood serum from four patients with inactive cirrhosis and from five patients with active chronic hepatitis and material obtained by liver biopsy on a patient with inactive cirrhosis were used.

Experiments were carried out on 118 CBA × C57BL hybrid male mice weighing 16-20 g. Two-thirds of the liver was resected by the method of Higgins and Anderson [6]. Liver extract, prepared by the method of Verly et al. [12], and blood serum were injected intraperitoneally into the mice in a dose of 1 ml/100 g body weight 26-27 h after the operation. The animals were killed 44-45 h after the operation. Hepatectomized mice were used as the control. Mitotic activity was determined by counting the number of mitoses in 3000 cells in histological sections. The significance of differences between the control and experiment was determined by the U test.

EXPERIMENTAL RESULTS

Blood serum of patients with inactive cirrhosis (Fig. 1A) induced considerable inhibition (by 74%) of mitotic activity in the mouse liver regenerating after partial hepatectomy. Extract of liver tissue from a patient with inactive cirrhosis had similar properties (Fig. 1B).

Blood serum from patients with active hepatitis also inhibited mitotic activity in the regenerating liver (Fig. 2) although, admittedly, in one case the inhibition was very little (by 16.7%), and differences between the control and experimental groups were not statistically significant ($P > 0.05$).

Recent observations have shown that cells produce special substances, known as chalones, which inhibit mitotic activity in the same tissue. It has been shown experimentally that liver extract of adult intact animals inhibits mitotic activity of hepatocytes in the regenerating liver [1, 2, 9, 10, 12-14].

A chalone-like effect of blood serum of adult intact animals also has been found [4, 5, 8, 10]. The present writers have demonstrated the presence of chalone in the morphologically unchanged human liver and in blood serum of clinically healthy persons [2]. Meanwhile, blood serum and extract of regenerating liver of animals have no such effect [1-3, 5, 11, 15].

It has been suggested [5, 10] that the mitosis-inhibiting factor is directly dependent on the quantity of tissue producing it. Partial hepatectomy reduces the quantity of functioning tissue, thus leading to a fall in the concentration of this factor both in the liver and in the blood serum, and in turn, this leads to active proliferation in the remainder of the liver.

It can be postulated on this basis that a similar situation arises in cirrhosis of the liver, for one of the leading signs of this condition is the formation of nodules of regeneration and a decrease in the mass of the parenchyma because of its replacement by connective tissue. Accordingly a decrease in the content of chalones might be expected in the cirrhotically changed liver, and absence of inhibition of mitosis in animals would be expected after injection of liver extract or blood serum from patients into them.

However, as the present investigation shows, blood serum and liver extract from patients with inactive cirrhosis led to considerable inhibition of mitotic activity in the regenerating liver, almost indistinguishable from that observed after injection of extracts of morphologically unchanged human liver and blood serum of clinically healthy persons. Meanwhile liver extract and blood serum from patients with active cirrhosis of the liver induced statistically significant stimulation of mitotic activity. The mitotic index of the experimental groups was 1.5-2 times higher than in the control [2].

It might be assumed that differences in the action of blood serum of patients with active and inactive cirrhosis on the regenerating liver were connected with differences in the character of the pathological processes in the liver tissue of these patients. One of the main morphological features of activity in cirrhosis is the presence of lymphoid-cell infiltration and of so-called staggered necrosis of the parenchyma of the liver. It might be supposed that death of the hepatocytes, which is constantly observed in the active form of cirrhosis, would lead to a decrease in the content of chalones and so determine the formation of new foci of regeneration.

A stimulating effect of some immunologic factors [7], such as γ-globulins, the concentration of which was increased in the blood of patients with active cirrhosis, would also have a stimulating effect on mitotic activity of the liver cells.

However, as Fig. 2 shows, blood serum of patients with active chronic hepatitis did not stimulate mitotic activity, although foci of infiltration of the portal tracts and staggered necroses were present in the liver tissue of these patients, just as in those with active cirrhosis, and similar immunologic changes were present, such as γ-globulinemia.

The mechanism of simulation of mitotic activity of hepatocytes revealed by this investigation is not yet completely clear. Judging from the fact that neither liver extract nor blood serum from patients with inactive cirrhosis of the liver and with active chronic hepatitis possesses properties such as these, it may be considered that the stimulating effect observed is due not only to the presence of regeneration and a decrease in the content of chalones in the liver of patients with active cirrhosis, but also evidently with the appearance of certain factors in the liver itself, which stimulate regeneration of the hepatocytes and take part in the morphogenesis of cirrhosis, promoting the formation of new nodules of regeneration. This response can be regarded as compensatory, but replacement of the hepatic parenchyma by nodules of regeneration leads to considerable functional disturbances. Moreover, the constant stimulation of regeneration processes may lead to the formation of hepatocellular carcinoma.

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