EXPERIMENTAL CIRRHOSIS OF THE LIVER PRODUCED BY DYSENTERY TOXIN

M. N. Khanin, L. A. Alimova, and M. K. Irgashev

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Chronic poisoning of albino rats by intravenous injection of dysentery toxin for 2-4 months led to the development of cirrhosis of the liver. Development of cirrhosis was particularly intensive if injection of the dysentery toxin was accompanied by very small doses of heliotrope, containing hepatotoxic alkaloids. The heliotrope was added to the animals' diet and given once every 7 days. The results are regarded as evidence of the etiological role of chronic intestinal toxico-infections in the development of cirrhosis of the liver.

Cirrhosis of the liver can develop as a result of the effects of toxico-infections. Epidemic hepatitis [2, 6, 9] and alcohol [4, 13-15] are regarded as important factors in the development of the disease. In about 30% of patients the cause of development of the cirrhosis cannot be established [3, 10]. Clinical observations suggest that chronic intestinal toxico-infections (enterocolitis, chronic dysentery, enzymic and putrefactive dyspepsias, nonspecific ulcerative colitis, etc.) play an important role in the etiology of cirrhosis of the liver. However, there is no accurate clinical observation or experimental evidence in support of this hypothesis.

The writers have carried out experimental investigations involving chronic poisoning of animals with dysentery toxin, consisting of a chilled, dried culture of Shigella shigae. Preliminary experiments were carried out to establish the experimental conditions. Tests were carried out on animals of different species (rabbits, dogs, rats) using various doses of toxin. Rats were found to be suitable for the chronic experiments.

EXPERIMENTAL METHOD

Experiments were performed on 27 female albino rats weighing 180-220 g, divided into three groups with nine animals in each group. The rats of group 1 received dysentery toxin (DT) in a dose of 0.0005 g per animal. The required dose of DT was carefully ground beforehand in an agate mortar with a few drops of physiological saline to obtain a homogeneous mass, and the mixture was then diluted with the same solution. This dose of toxin was injected intravenously in a volume of 1 ml once every 10 days for 2 months. The dose of DT was then reduced by half, to 0.00025 g, and this dose was injected every 15 days for a further 2 months. The total duration of DT administration was 4 months. The animals of group 2 received heliotrope seeds with their diet, a procedure which has been shown to cause the development of cirrhosis of the liver [11, 12]. The heliotrope was mixed with the food in a concentration of 3% by weight and given once every 7 days for 4 months. The animals of group 3 received DT together with heliotrope seeds. The doses of DT and heliotrope corresponded to those in the previous groups. On the 65th-70th day of the experiment liver biopsy was performed on all the animals. The pieces of liver tissue were examined under the microscope. Administration of heliotrope and DT was terminated on the 120th day because of death of some of the animals (62nd-125th days of the experiment). Liver biopsy was repeated on the remaining rats on the 208th day; on the 225th day all the animals were sacrificed. The blood and organs were investigated by biochemical and morphological tests.

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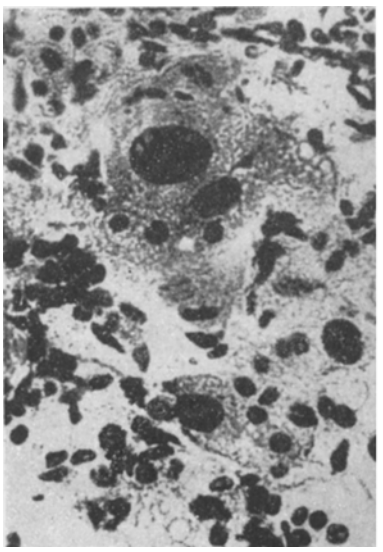

Fig. 1

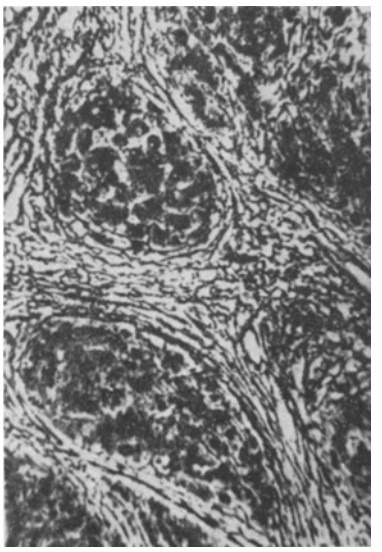

Fig. 2

Fig. 1. Hypertrophy of hepatocytes and marked cellular infiltration. Photomicrograph, hematoxylin-eosin, 400 times.

Fig. 2. Cirrhosis of the liver with the formation of pseudolobules. Photomicrograph, silver impregnation by Donskii's modification of the Bielschowsky-Gros method, 56 times.

TABLE 1. Summarized Results of Investigations

Toxic agent	No. of animals			
	total	dying	surviving and sacrificed	with cirrhosis of the liver
DT	9	5	4	4
Heliotrope	9	6	3	3
DT plus heliotrope	9	7	2	8

EXPERIMENTAL RESULTS

In the animals of group 1 severe damage to the liver tissue under the influence of DT administration was observed on the 65th day. Against the background of marked disturbances of the circulation, some of the animals showed foci of necrosis of the hepatic lobules, usually around the central veins, with marked round-cell infiltration, degeneration of the cytoplasm of the hepatocytes, and pycnosis or hypertrophy of their nuclei (Fig. 1). Later these animals exhibited typical cirrhotic changes with disturbance of the lobular structure, the presence of nodules of regeneration, intralobular proliferation of connective tissue, and detachment of a group of hypertrophied hepatocytes or of solitary cells of this type (Fig. 2). Other animals showed merely a well-marked degeneration of the cytoplasm with no accompanying regenerative or inflammatory changes.

Changes of a similar type in the liver were observed in the animals of group 2 which received small doses of heliotrope. However, the severest damage to the liver was observed in the animals of group 3, exposed to the simultaneous action of DT and heliotrope. Cirrhosis of the liver was found in nearly all the animals of this group (Table 1).

The simultaneous action of DT and heliotrope reflects a situation similar to the combined assault on the human organism when an infectious disease of the intestine is superposed on existing toxic damage to the liver (hepatitis, fatty degeneration of the liver, etc.). The experiments thus showed that severe

degenerative and inflammatory changes arise in the liver of animals exposed to chronic poisoning with dysentery toxin, and some of the animals develop the typical picture of cirrhosis of the liver.

When giving dysentery toxin, it was not intended to give the animal "dysentery". Any such attempts have so far proved unsuccessful [1, 5, 7, 8]. Poisoning with dysentery toxin was regarded as a pathological state in which the actual agent of the disease itself is not essential. Dysentery in man is a disease with this type of picture. Besides the extensive Shigella group, dysentery can also be caused by parasitic bacilli, Bacillus pyocyaneus, Proteus, hemolytic streptococci, staphylococci, and so on. Dysentery is thus a type of response of the organism to a wide variety of microbiological factors [16].

It is the "various microbiological factors" of this type which are characteristic of the chronic lesions of the intestine whose course is accompanied by absorption of bacterial exotoxins and endotoxins as well as the products of putrefactive and enzyme dyspepsias. If this type of poisoning is sufficiently intensive and prolonged, it is accompanied by damage to the liver, which may range from structural and functional disturbances of the organ to the development of cirrhosis.

The results of these investigations provide convincing experimental proof of the role of chronic toxico-infectious lesions of the intestine in the etiology of cirrhosis of the liver. No reference could be found in the literature to investigations of this type.

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