ROLE OF THE LYMPHOID CELLS OF THE IMMUNE SYSTEM IN THE GENESIS OF LIVER DISEASES

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Experiments on CBA×C57BL mice showed that a mixture of bone marrow, thymus, and spleen cells from donors with experimental hepatitis induced by carbon tetrachloride, and also from donors after resection of one-third of the normal liver, if injected into healthy animals, led to degenerative changes in their liver. This points to the presence of a special clone of cells with a harmful hepatotropic action, which participate in the mechanisms of autoimmune disturbances in liver diseases.

KEY WORDS: lymphoid cells; hepatitis; resection of the liver; autoimmune injuries.

Evidence of the important role of the lymphoid tissue in the regulation of the number and quality of the cells of organs has recently been published [1, 6, 7]. Attempts have been made to produce experimental hepatitis by transplanting lymphocytes from the spleen or lymph nodes of animals with toxic heliotrine hepatitis [2, 3, 8]. However, the use of noninbred animals [2] and of immunodepressive agents [3] in these experiments and transplantation of cells from the spleen or lymph nodes alone did not permit the role of the lymphocytes to be established in the pathogenesis of autoimmune processes in chronic diseases of the liver, for data obtained in recent years have indicated a close functional connection between bone marrow and thymus cells and the peripheral lymphoid organs [5].

The object of the present investigation was accordingly to study changes in the recipient's liver after transplantation of a mixture of bone marrow, thymus, and spleen cells from donors with experimental hepatitis, from donors with resection of one-third of the normal liver, and from intact donors, in experiments on inbred animals.

EXPERIMENTAL METHOD

Experiments were carried out on 49 CBA×C57BL mice weighing 25-27 g. Experimental hepatitis was induced by subcutaneous injections of carbon tetrachloride (0.2 ml of a 60% solution on alternate days) for 2 weeks. The animals were killed and the bone marrow, thymus, and spleen removed under sterile conditions. Cells of the organs were obtained by the usual method [4] with medium No. 199. A suspension of cells was prepared. The tissue was cut into small pieces with scissors and passed through injection needles of decreasing diameter. Suspensions of bone marrow, spleen, and thymus cells were filtered through Kapron gauze and centrifuged for 10 min at 100 rpm. The supernatant was poured off and medium No. 199 added to the cells. Each suspension contained $2 \cdot 10^6$ viable cells in 0.5 ml. Carefully mixed suspensions of bone marrow, thymus, and spleen cells were mixed in equal proportions and 0.5 ml of the mixture was injected into the caudal vein of a healthy recipient (16 animals). A mixture of bone marrow, thymus, and spleen cells was obtained in the same way from donors after resection of one-third of the normal liver and from intact animals. Healthy mice of one group (11) received an injection of a mixture of cells from animals with resection of the liver, and another group (10) received a mixture of bone marrow, thymus, and spleen cells from intact animals. The mice were killed 24, 48, and 72 h after transplantation. Pieces of liver were fixed in 10% neutral formalin. Paraffin sections 5μ thick were stained with hematoxylin–eosin.

EXPERIMENTAL RESULTS

The liver of all recipients of a mixture of cells from animals with experimental hepatitis 24 h after transplantation was pale brown in color. Marked diffuse granular degeneration of the hepatocytes was detect-

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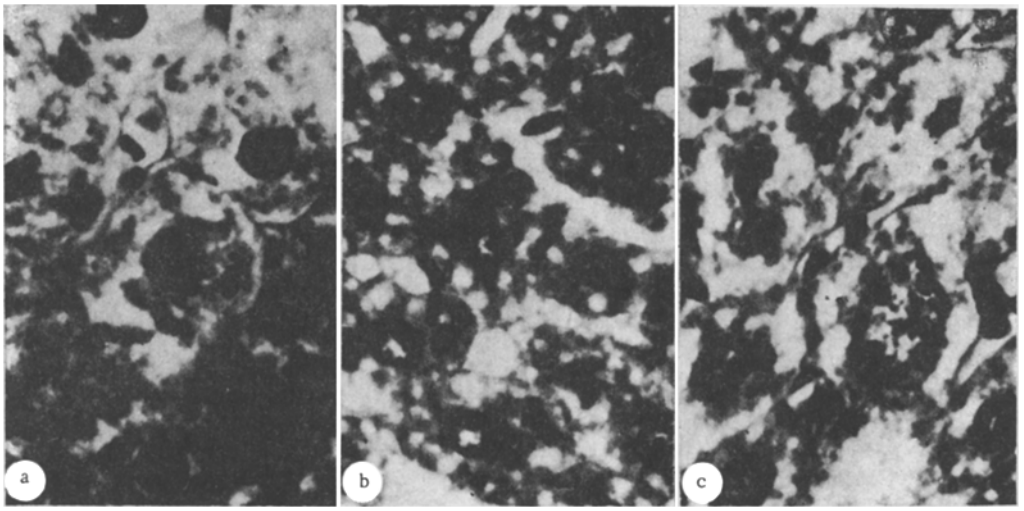

Fig. 1. Liver of CBA × C57BL mice receiving a mixture of bone marrow, thymus, and spleen cells from donors with experimental hepatitis: a) 24 h, b) 48 h, c) 72 h after transplantation. Hematoxylin–eosin, 600×.

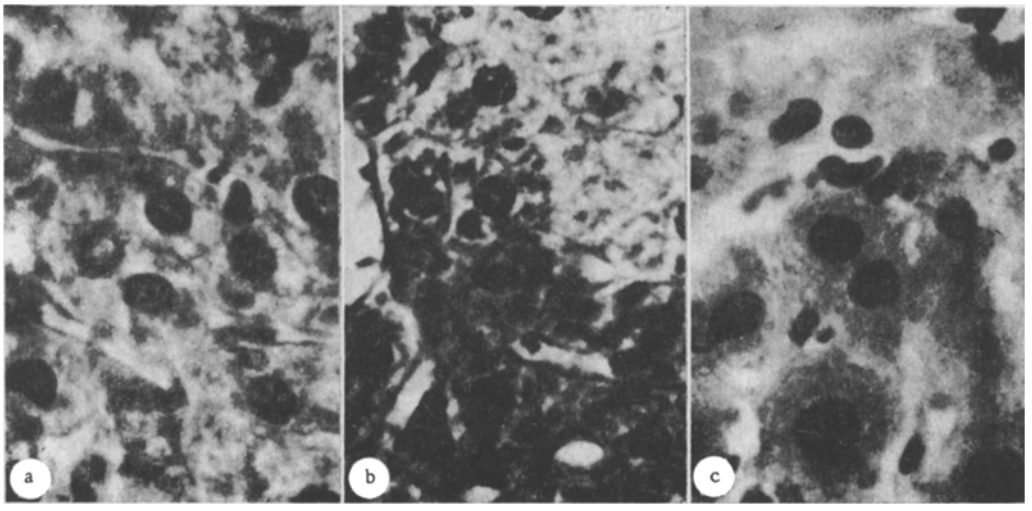

Fig. 2. Liver of CBA × C57BL mice receiving mixture of bone marrow, thymus, and spleen cells from donors with resection of the liver and intact animals: a) 48 h, b) 72 h after transplantation of cells from animals with resection of the liver; c) recipient's liver 72 h after injection of cells from intact animals. Hematoxylin–eosin, 600×.

able microscopically (Fig. 1a). Polymorphism of the liver cells and their nuclei and nucleoli in size and shape was observed, with anisochromia and lymphoid infiltration along the course of the portal tracts.

The recipients' liver after 48 h showed marked intracellular edema (Fig. 1b); vacuoles of different sizes appeared in the cytoplasm and nuclei of the liver cells.

Degenerative changes in the liver were still considerable after 72 h (Fig. 1c). Large vacuoles frequently occupied the whole cytoplasm of the hepatocyte and swelling, vacuolation, and pycnosis of the nuclei and death of the liver cells were observed. Along the course of the vascular tracts round-cell infiltration could be seen.

Degenerative changes in the liver also were observed in recipients receiving a mixture of lymphocytes from donors with resection of one-third of the normal liver. The severity of the pathological changes in the organ was much less than in the previous series of investigations. The changes in the hepatocytes resembled granular degeneration (Fig. 2a, b). At the same time, extensive areas of unchanged liver tissue were observed.

No degenerative changes could be seen in the liver of mice receiving a mixture of bone marrow, thymus, and spleen cells from intact animals.

These investigations thus showed that transplantation of a mixture of cells of organs of the immune system (bone marrow, thymus, and spleen) from donors with experimental hepatitis and resection of the liver causes degenerative changes in the liver of healthy recipients. This indicates the existence of a special clone of cells with a harmful hepatotropic action. The degree of injury to the liver varies. A mixture of lymphocytes from animals with experimental hepatitis carried more pronounced morphogenetic information on cell damage and development of pathological changes than cells from mice with resection of the liver. Damage to hepatocytes obtained under these experimental conditions on inbred animals suggests that organs of the immune system participate in the pathogenesis of autoimmune lesions in hepatitis and cirrhosis of the liver.

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