In response to injection of tetanus toxin a unique response of the HHNS thus develops; activation of the system is evidently explained by injection of the heterologous protein, for a similar effect is given by injection of the inactivated toxin. Changes in the clotting system of the blood, lipid metabolism, and vascular permeability are noteworthy.

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EFFECT OF CYTOTOXIC IMMUNE SERA ON FORMATION OF FOCI OF HEMATOPOIESIS (MICROCOLONIES) IN THE MOUSE SPLEEN

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Injection of antierythrocytic or antithrombocytic immune serum into unirradiated mice stimulates the formation of foci of hematopoiesis (microcolonies) in the spleen. It is suggested that the formation of microcolonies by stem cells is not specific for the irradiated organism.

KEY WORDS: hematopoiesis; cytotoxic sera.

A few days after irradiation of mice foci of hematopoiesis, or microcolonies, are formed in certain parts of the spleen [3, 4]. Whether this phenomenon is characteristic of irradiated animals only or not is an interesting question. There are data in the literature [1, 2] to show that foci of myelopoiesis can be formed in the lymph nodes after injection of sarcolysin (phenylalanine mustard) and foci of myelo- and erythropoiesis in the liver after injection of cyclophosphamide. Microcolony formation in hematopoietic organs, including the spleen, is evidently connected with an acute deficiency of blood cells in the body, with the consequent activation of hematopoiesis.

To verify this hypothesis, a deficiency of erythrocytes or platelets was induced in mice and hematopoiesis was subsequently activated by injection of the corresponding cytotoxic immune sera.

EXPERIMENTAL METHOD

Experiments were carried out on 80 noninbred albino mice and inbred CBA mice weighing 20-24 g. In series I the animals were given three or four intraperitoneal injections of cytotoxic immune serum, agglutinating erythrocytes (AES) or platelets (ATS) of mice in a titer of 1:8, in a dose of 0.15 ml (diluted 1:20) at intervals of 24 h. The serum was obtained after three injections of $5 \cdot 10^8$ mouse erythrocytes or platelets into rabbits. The first injection was given intradermally (with Freund's complete adjuvant) and subsequent injections intravenously at intervals of 4 weeks. The sera obtained on the 7th day were exhausted with serum,

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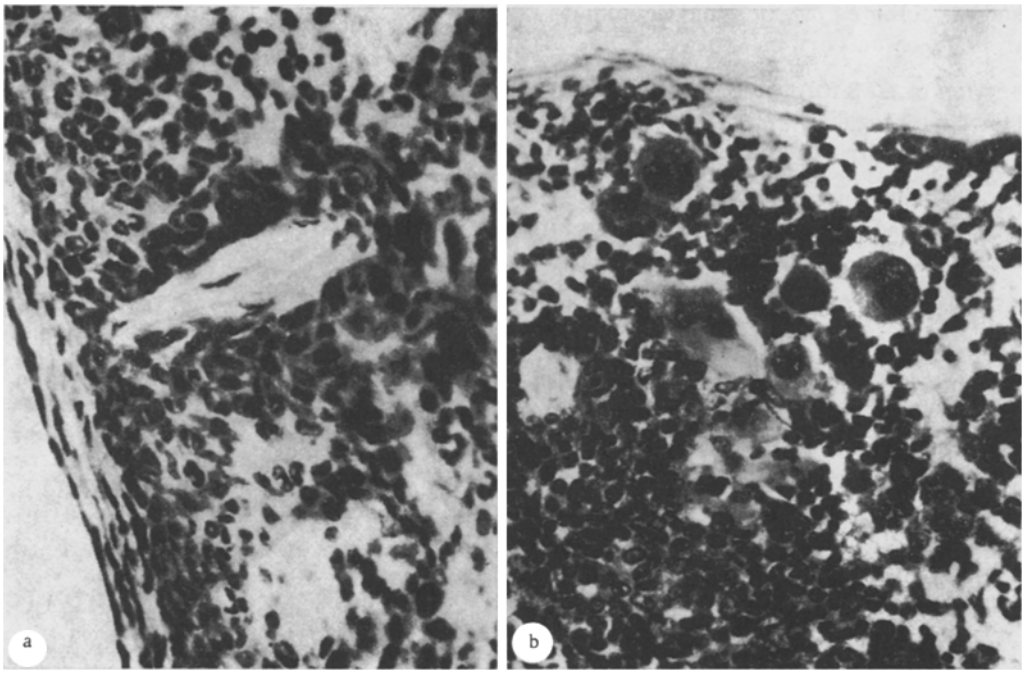

Fig. 1. Spleen of mouse 7 days after injection of antierythrocytic immune serum. Colonies of granulocytic (a) and megakaryocytic (b) type. Hematoxylin–eosin, 120×.

homogenates of lymph nodes and thymus, and a suspension of peritoneal macrophages, all from mice. The ATS in addition was exhausted with erythrocytes. After injection of ATS into the animals the platelet count in the peripheral blood was reduced by 90%, and the injection of AES and caused their erythrocyte count to fall by 64%.

The animals were killed 7 days after the last injection and their spleen investigated.

In the experiments of series II, 24 h after the third injection of one of the cytotoxic sera, CBA mice were given an intravenous injection of 10^5 nucleated syngeneic bone marrow cells from intact animals, and the spleen was investigated 7 days later.

In all cases intact mice and mice receiving the same number of injections of physiological saline or of normal rabbit serum, diluted 1:20, served as the control.

EXPERIMENTAL RESULTS

After injection of physiological saline or normal rabbit serum into the animals no changes were found in the spleen.

In the spleen of mice killed 7 days after the third injection of AES or ATS, some loosening of the structure of the red pulp and a decrease in its cell content were observed. In the subcapsular zone discrete foci of granulocytic (Fig. 1a) and megakaryocytic (Fig. 1b) hematopoiesis were visible in the form of groups of cells of different degrees of maturity. These groups resembled the microcolonies that can be found histologically in the spleen of irradiated mice [4]. Usually up to 30 or 40 colonies could be found in a longitudinal section through the spleen. Cells of the erythroid series were diffusely distributed in the zone of the red pulp.

After the fourth injection of cytotoxic sera the red pulp was depopulated even more, and there were far fewer cells of the erythroid and megakaryocytic series than at the first examination. Most cells were granulocytes at different stages of maturity, chiefly metamyelocytes. Foci of granulocytic hematopoiesis were much larger in size than after the third injection. The microcolonies were so numerous that they frequently merged to form bands of granulocytic cells along the capsule of the spleen.

The morphological changes in the spleen after injection of the two cytotoxic sera were thus stereotyped in nature and consisted of a reduction in the number of cells in the red pulp and the formation of foci of hematopoiesis (microcolonies). In experiments in which bone marrow was transplanted into animals after injection of ATS, diffuse proliferation of cells of the megakaryocytic and erythroid series was found in the red pulp

of the spleen and all colonies of granulocytic hematopoiesis were present in the subcapsular zone. The number of megakaryocytes was very considerable: up to 20 per field of vision in the sections (140×).

After injection of AES followed by bone marrow, proliferation of cells of the erythroid series was more marked and that of the megakaryocytic series less marked than after injection of ATS. Foci of hematopoiesis consisting of cells of all three series (colonies of mixed type) were found in the subcapsular zone.

The results of these investigations show that foci of hematopoiesis (microcolonies) may be formed in the spleen of unirradiated mice after repeated injections of immune cytotoxic sera. The formation of microcolonies connected with the functioning of hematopoietic stem cells is evidently not specific for the irradiated organism.

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ULTRASTRUCTURAL AND FUNCTIONAL REVERSIBILITY OF SCLEROTIC CHANGES IN THE RAT LIVER CAUSED BY EXOGENOUS ORGAN-SPECIFIC RNA

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The ultrastructure of parenchymatous and stromal cells was studied in relation to reversibility of experimental cirrhosis of the liver in rats under ordinary conditions and also under the influence of exogenous RNA administered in various ways. The dynamics of the changes in cell ultrastructure correlated with the dynamics of the quantitative indices. A short course of RNA was found to have a beneficial role on intracellular reparative regeneration of the hepatocytes, but a long course had an adverse effect. Both parenchymatous and stromal cells take part in the resorption of collagen.

KEY WORDS: reversibility of cirrhosis of the liver; effect of exogenous RNA; ultrastructure and function; parenchyma and stroma; resorption of collagen.

Several workers have demonstrated the reversibility of sclerotic changes in the liver [8, 12, 14]. An important role in the resorption of collagen is ascribed to the cells both of the parenchyma and of the stroma of an organ, including Kupffer cells [6, 8, 10, 14, 15]. However, the mechanism of resorption of the excess of fibrous tissue has not been finally elucidated.

One of the main metabolic processes concerned in the regeneration of the pathologically changed organ is protein biosynthesis programmed by nucleic acids. The ability of exogenous nucleic acids or their hydrolysis products to stimulate regeneration has been demonstrated [5, 9-11]. Nevertheless, this problem continues to provoke discussion. The effect of nucleic acids on the subcellular manifestations of reparative regeneration of the liver has not been studied at all.

In this investigation the reversibility of the subcellular changes and indices of the protein-synthesizing function of the cirrhotic liver were studied at different stages of regeneration of the organ under ordinary conditions and under the influence of exogenous organ-specific RNA.

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