MORPHOLOGICAL CHANGES IN THE LIVER CAUSED BY Sr^{90}

G. A. Lebedeva

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Recently considerable attention has been paid to the study of the biological action of strontium-90 (Sr^{90}), a product of uranium fission, because this isotope readily enters the body, is retained in the skeleton for a long time, and has a long half-life period (T = 25 years).

The effect of Sr^{90} on the skeleton [2, 5, 12] and bone marrow [1, 20] has now been studied in considerable detail. The changes in other organs, including the liver [3], have been examined less fully. However, reports have been published indicating that functional disturbances may arise in the liver tissue following administration of this isotope [15].

The object of this investigation was to study the morphological changes arising in the liver following administration of Sr^{90} to animals of different species and to analyze some of the mechanisms of development of the pathological process in this organ.

EXPERIMENTAL METHOD

Experiments were carried out on the liver of 20 dogs and 145 albino rats. The isotope was injected intravenously into the dogs in a single dose of 0.1-0.2 μCi/g, and also given by mouth as a single dose of 0.5 μCi/g or daily for 6 months in a dose of 1 μCi/kg body weight. The rats received Sr^{90} by intraperitoneal injection in doses of 0.05, 0.1, or 0.5 μCi/g. The control group consisted of 5 dogs and 40 rats. The liver of the experimental animals was investigated at various times after the beginning of the experiment (from 1 day to 2 years in the case of the rats and to 5.5 years for the dogs). The material was fixed in 10% neutral formalin solution and embedded in paraffin wax. Histological sections were stained with hematoxylin–eosin and by Van Gieson's method or impregnated with silver by Foot's method. Frozen sections were stained with Sudan III. The total tissue dose was also calculated for the liver, using toxicological data [7] obtained in experimentals carried out in conditions analogous to those of the present experiments.

EXPERIMENTAL RESULTS

Morphological investigations of the dogs' liver 1-3 days after receiving Sr^{90} showed only a transient hyperemia of the liver tissue. In the period of exacerbation of the disease (3rd-5th weeks), besides disturbance of the circulation in the center of the lobules, signs of cloudy swelling and fatty degeneration of the liver cells appeared. Later, after a period when the animal remained reasonably well (6 months), obvious morphological changes again developed in the liver tissue. The most marked disturbances were found after 7-66 months, when the animals developed leukemia, tumors of the skeleton, or aplastic processes in the hemopoietic organs.

In rats, unlike the dogs, these phases of development of the changes could not be demonstrated. For a long time after administration of the Sr^{90} (up to 5 months) cloudy swelling or fatty degeneration of the liver cells was observed only in a few animals. More severe changes, as in the dogs, were found in the later periods after administration of the isotope (after 6-24 months), when the rats developed tumors of the skeletal bones, leukemia, hypoplasia of the hemopoietic organs, and chronic inflammatory processes in the intestine or lungs. The severity of the liver lesion in both species of animals did not depend on the dose of isotope, but on the character of development of the pathological process in the body.

With the appearance of bone tumors or hypoplasia of the hemopoietic organs in the rats, a moderately severe cloudy swelling of the liver cells of the central portions of the lobules appeared. In the dogs, besides the degenerative changes, circulatory disturbances very often developed (Fig. 1a), and sometimes atrophy of the liver cells could be seen in the center of the lobules, with the formation of islands of fatty degeneration of the liver or ingrowth of connective tissue (Fig. 1b).

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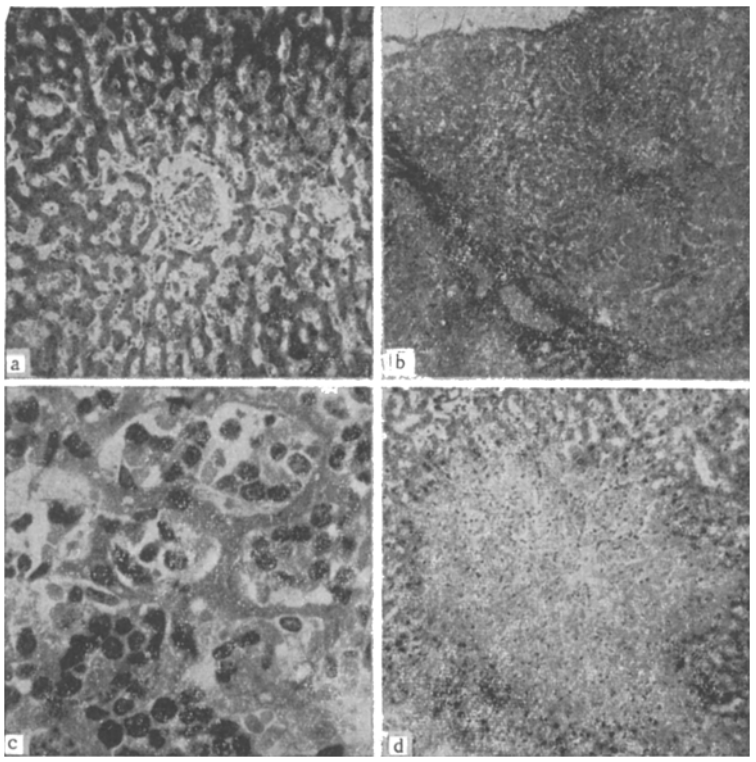

Fig. 1. Morphological changes in the liver of dogs and rats following administration of Sr^{90}. a) Liver of a dog 9 months after intravenous injection of 0.2 μCi/g. Disturbance of the circulation with the development of perivascular edema around the central vein. Photomicrograph. Hematoxylin–eosin. 140×; b) liver of a dog 2.5 years after repeated oral administration of Sr^{90} in a dose of 1 μCi/kg. Proliferation of connective tissue with the formation of pseudolobules. Photomicrograph. Van Gieson. 70×; c) liver of a rat 10 months after intraperitoneal injection of 0.1 μCi/g. Diffuse leukemic infiltration with atrophy of liver cells. Photomicrograph. Hematoxylin–eosin. 630×; d) liver of a rat 1 year 8 months after intraperitoneal injection of 0.05$\mu\mu$Ci/g. Necrosis of liver tissue in the center of the lobule. Photomicrograph. Hematoxylin–eosin. 100×.

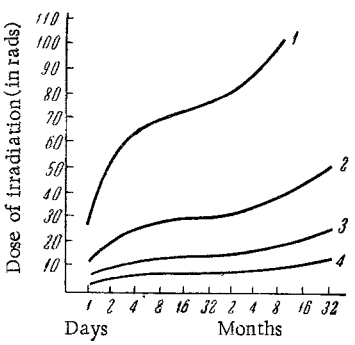

Fig. 2. Total tissue dose for the liver at different times after administration of Sr^{90}. 1) 0.5 μCi/g; 2) 0.2 μCi/g; 3) 0.1 μCi/g; 4) 0.05 μCi/g.

More marked disturbances were found during the development of leukemia, when besides degenerative changes, focal or diffuse leukemic infiltration appeared in the liver of both groups of animals (Fig. 1c), and in some cases proliferation of connective tissue was observed. In most of the rats and some of the dogs, areas of necrosis were found in the center of the liver lobules. Meanwhile in the rats, the total number of the liver cells was reduced but their size was increased, with the formation of giant forms, indicating changes in the course of regeneration in the parenchyma of the organ. These changes were not found in the dogs.

In the liver of the rats, during the development of chronic inflammatory changes in the intestine and especially in the lungs, besides degenerative and sclerotic changes disturbances of the circulation could be observed. In these cases, in the animals

which died areas of necrosis of the liver cells were usually found in the center of the lobules, frequently involving large areas of the parenchyma of the organ (Fig. 1d). Similar changes were present in the control animals dying at the age of 1.5-2 years from chronic bronchopneumonia or bronchiectasis, but in these animals the areas of necrosis were less extensive and were found only half as frequently as in the experimental animals.

The development of necrosis of the liver during the action of ionizing radiation has been reported in the literature. Necrotic changes in the liver tissue may arise either during irradiation from external sources [6, 13, 16], or after introduction of radioactive isotopes into the body [10, 14, 18]. In poisoning with Sr^{90}, one of the causes of the development of necrosis in the liver may evidently be the disturbance of the circulation and hypoxia, although in individual cases its genesis is uncertain. It is also possible that after administration of Sr^{90}, the reactivity of the liver tissue is depressed, as is the case in the gastrointestinal tract [47].

It may be concluded from these results that following administration of Sr^{90} to animals of different species, the reaction of the liver tissue obeys certain general principles. The most marked disturbances arise in the late stages after administration of the isotope. They are localized mainly in the center of the lobules and they are degenerative in character, although in the more severe cases disturbances of the circulation and atrophic, necrotic, and sclerotic changes are added. Within the range of doses used, the severity of the lesion depends not on the dose but on the character of development of the pathological process in the body as a whole.

However, besides the general principles of development of the morphological changes in the liver, some aspects of the lesion were dependent on the species of the animals. For example, during the development of bone tumors or aplasia of the hemopoietic organs, the changes in the liver were more marked in in the dogs than in the rats. In addition, in the rats the phases of development of the disturbances could not be found, as in the case of the dogs. Meanwhile, in the liver of the rats developing leukemia, giant liver cells appeared and these were not found in the dogs. No such cells were found during the examination of the liver of dogs with cirrhotic changes after administration of cerium-144.

The question of the mechanisms of development of the pathological changes in the liver during Sr^{90} poisoning is of considerable interest. Following its introduction into the body, this isotope quickly leaves the soft tissues and remains fixed for a long time in the skeleton [7, 17, 19]. The results of calculation of the total tissue dose for the liver following administration of, for example, 0.2 μCi/g of Sr^{90} demonstrate that its value increases significantly only during the first week after administration of the isotope (to 28.6 rads by the 8th day), while in the period from 2 to 3 years it increases only by 3.4 rads, reaching 52.5 rads at the end of the 3rd year (Fig. 2). Meanwhile the morphological changes in the liver become more evident at a time when the total tissue dose is not increasing. It could be postulated that the liver tissue, like other slowly renewed tissues, "remembers" and summates the radiation effects, as has been demonstrated in the case of bone tissue [8, 9]. However, the small magnitude of the total tissue dose, and also the relationship discovered in the present investigation between the severity of the lesion and the character of development of the pathological process in the body as a whole, suggest that the indirect effect of Sr^{90} on the development of morphological changes in the liver tissue is very important.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.
