The suggested preparation thus restores the basic parameters of the hemodynamics and gas exchange well, when disturbed after blood loss, and it can be recommended as the basis for a combined plasma expander and oxygen carrier.

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TOXIC ACTION OF DITHIZONE ON INSULIN-PRODUCING CELLS

Academician I. V. Toroptsev* and V. A. Eshchenko

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KEY WORDS: Islets of Langerhans; zinc; chelating agents; dithizone; structural damage.

Interest in the toxic action of chelating agents on cells is due not only to advances in the fundamental sciences, but also to purely practical problems. These agents are being increasingly used in agriculture, in various branches of industry, and in medicine [6, 7, 9]. It has been shown that administration of the powerful chelating agent dithizone to rabbits causes necrosis of the B-cells of the pancreatic islets and the development of permanent diabetes [4, 8, 9]. The mechanism of these changes has been studied [5].

The object of this investigation was to compare the toxic action of dithizone on insulin-producing cells in animals at different levels of evolutionary development.

EXPERIMENTAL METHODS

Altogether 320 animals of different species were used (fishes, frogs, pigeons, mice, guinea pigs, golden hamsters, rats, rabbits, cats, and dogs).

Dithizone was injected intravenously and intra-arterially (fishes) in doses of 50-100 mg/kg as a 1% solution in 0.5% ammonia solution. The animals were killed from 3 min to 5 days after the injection. Frozen sections were cut from pieces of pancreas and fixed in Bouin's fluid, in acetone, and by Timm's method.

For the morphological investigation paraffin sections were stained with hematoxylin and phloxine by Gomori's method. The specific granules of the insulin-producing cells were revealed by means of aldehyde fuchsin. Zinc was detected by staining sections with dithizone and with 8-(p-tosylamino)quinoline (8-TQ) [1, 2]. Sections also were fluorochromed with chlorotetracycline (to detect calcium bound with hydrophobic sites in the cells) and with acridine orange (for the metachromatic reaction) [3]. To excite luminescence UFS-3 and FS-1 filters were used, in conjunction with ZhS-3 and ZhS-18 filters for protection.

*Academy of Medical Sciences of the USSR.

Department of Pathological Anatomy, Tomsk Medical Institute.

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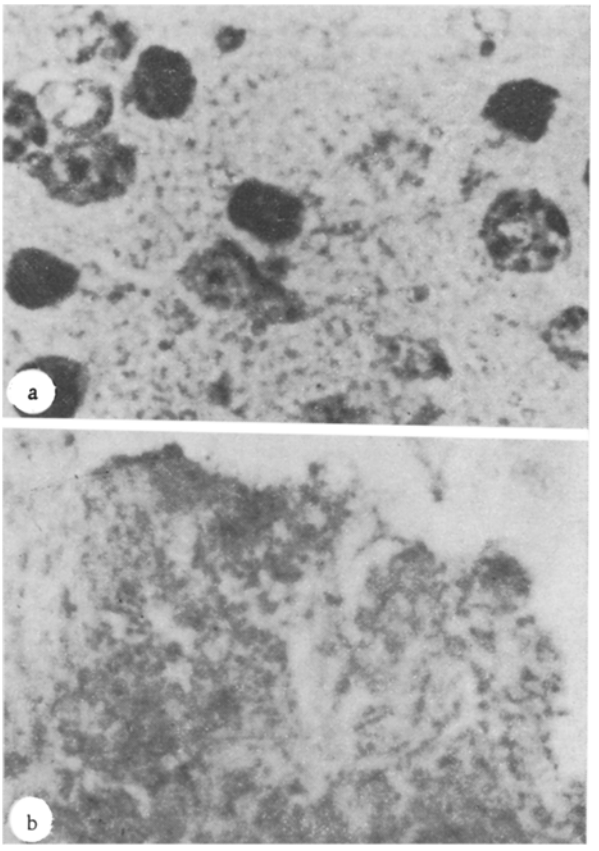

Fig. 1. Necrosis of B-cells of pancreatic islets in mouse treated with dithizone. a) Hematoxylin and phloxine, b) aldehyde fuchsin by Gomori's method. 900 ×.

EXPERIMENTAL RESULTS

In sections stained with aldehyde fuchsin, bluish-violet granules were observed in the cytoplasm of the insulin-producing cells; they were most numerous in rodents and least in dogs, pigeons, and frogs. Green fluorescence of the B-cells in sections stained with chlortetracycline was best revealed in mice. The metachromatic reaction with acridine orange was present in these cells in the form of red luminescence.

In sections stained with dithizone, purplish-red granules were found at sites of weakly bound zinc, and in the dark field of the microscope they gave orange-red luminescence. 8-TQ gave green luminescence with zinc. A positive reaction for zinc was detected in the cytoplasm of the cells but not in the region of the nucleus. Most zinc was found in the pancreatic B-cells of rabbits, hamsters, and mice, least in rats, but in guinea pigs no zinc whatever was found in the pancreatic islets.

Injection of dithizone into the animals caused the development of an intravital histochemical reaction at sites of weakly bound zinc. Electron-microscopic [10] and spectrophotometric investigations have shown that the product of this reaction is zinc dithizonate, and that it is localized in membranous sacs surrounding mature secretory granules in the cells. It was there that the earliest histochemical changes were observed. The decrease in the content of histochemically detectable metals and of aldehyde-fuchsin granules, reflecting the insulin content in the cells, and intensification of the metachromatic reaction with acridine orange was found in a few minutes after the injection. Typical signs of necrosis (pycnosis, rhexis, lysis of the nuclei, etc.) were found after 1-2 h and reached maximal intensity after 8-48 h (Fig. 1). The development of necrosis was accompanied by further weakening of the reactions for zinc and led in severe cases to total disappearance of these reactions from the cells. The severest damage was suffered by insulin-producing cells in rabbits, hamsters, and mice, less severe by rats, and in guinea pigs no pathological changes whatever could be observed in these cells.

Comparative studies revealed a clear parallel between the concentration of intravitally formed zinc dithizonate in the cells, the duration of its stay there, and the degree of damage to these cells. In animals treated with powerful nucleophilic agents, the toxic action of this complex in the pancreatic B-cells was weakened.

The results of these experiments confirm the previous hypothesis that the mechanism of the pathological action of dithizone and other chelating agents on insulin-producing cells is based on the formation of an unsaturated (electrophilic) complex with zinc in them [5].

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STEREOLOGIC ANALYSIS OF MYOCARDIAL STRUCTURES IN PLASTIC CARDIAC INSUFFICIENCY (ABNORMAL ULTRASTRUCTURAL CARDIOMYOCYTE REGENERATION)

L. M. Nepomnyashchikh, D. E. Semenov, V. P. Tumanov, and Yu. G. Tsellarius

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KEY WORDS: Plastic cardiac insufficiency; myocardial parenchyma and stroma; cardiomyocyte ultrastructure; stereology.

Plastic insufficiency of the heart is associated with a disturbance of reproduction of the intracellular structures of cardiomyocytes, and it is to be distinguished from alterative myocardial insufficiency which develops as a result of injury to the muscle cells and the exclusion of some of them from contractile activity [2, 6]. The ultrastructural manifestations of plastic insufficiency were studied by the writers in experiments to determine the depression of protein synthesis in cardiomyocytes of albino rats treated with the anthracycline antibiotic rubomycin [5].

The object of the present investigation was a stereologic analysis of the myocardium in the same model in order to elucidate the role of cardiosclerosis in the development of plastic insufficiency of the cardiomyocytes.

EXPERIMENTAL METHODS

Eighteen male Wistar rats weighing 160-180 g were used. Rubomycin hydrochloride (0.2% solution) was injected intraperitoneally into nine rats in a single dose of 30 mg/kg body

Department of Pathomorphology and Morphometry, Institute of Clinical and Experimental Medicine, Siberian Branch, Academy of Medical Sciences of the USSR. Laboratory of Pathomorphology, Institute of Cytology and Genetics, Siberian Branch, Academy of Medical Sciences of the USSR, Novosibirsk. Department of Pathological Anatomy, A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR, Moscow.

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