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REDUCTION OF PRESSURE IN ARTERIAL VESSELS AS AN ANTITUMORAL EFFECT

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It was found experimentally that reduction of arterial pressure causes changes in hemodynamics in tumoral tissue, and retardation of growth and death of malignant cells is a secondary effect resulting from the violation of microcirculation and transcapillary transfer.

At present there is the potential possibility to cure only 33% of localized tumors. 17% of them are cured by radiotherapy, 15% by operations, and 1% by chemotherapy [1]. The problem of overcoming numerous medicinal resistances of tumors remains unsolved [2]. Therefore, the search for new means and methods of improving the efficiency of antitumoral therapy is still a very urgent problem. One of the promising ways in this direction is the employment of antitumoral effect of arterial hypotension, which was for the first time discribed by one of the authors [3].

For this purpose the antitumoral effect of sarcolysine was studied. The treatment by this preparation was conducted against the background of constant reduction of pressure in arterial vessels. In the second series of experiments the effect of repetitive seances of controlled medicinal hypotension was studied. The experiments were conducted in 96 stock-bred laboratory albino Wistar rats who had a body mass of 150–200 g. All the experiments graft sarcoma 45 (Sa-45).

1. Enhancement of the Effect of Sarcolysine in Arterial Hypotension. The conditions of stable arterial hypotension in experimental animals were provided by the earlier described technique [3]. Homogenate Sa-45 was injected to the femur muscle by the commonly adopted technique a week after hypotension was established. After two weeks of grafting, half of the control and all the experimental animals were subject to chemotherapy. 3 mg/kg of sarcolysine, that is a half of a medicinal dose, were injected intraperitoneally in 72 hours. 7 injections were made altogether in three days after the last injection of the chemical preparation animals were killed, and tumors were removed, weighed and kept in 10% solution of formalin. Parafinic sections were stained with hematoxyline-eosin and nicrofuxine (see Table 1).

As is seen, the retardation of the growth of tumors under the effect of half of the medicinal dose of sarcolysine is most vividly expressed in animals with arterial hypotension. This result indicates that reduction of intravascular pressure not only prevents the preparation from getting into the blastoma tissue, but also strengthens its therapeutic effect.

It is revealed in microscopic studies of tumors subjected to chemotherapy under the conditions of arterial hypotension that those tumors were, as a ruled, formed of small nodules separated by layers of conjunctive tissue. In the center of each nodule there were converging necrosis nodules. In the peripheral portions of tumors small focuses of decay were also found. The character of dystrophic changes in malignant cells and the predominance of medicinal pathomorphism in the portions with tissue fibrosis were similar to those in tumors with normotension. In one of tumors a complete resorption of neoplastic cells took place; a granulation tissue with rich polymorphocellular infiltration grew at that place.

* Deceased.

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TABLE 1. Mass of Tumours in Animals with Normal and Reduced Arterial Pressure in Treatment with Sarcolysine (3 mg/kg, 7 intraperitoneal injections with an interval of 72 h)

Observation group	Number of animals	Mass of tumors by the end of observations (g)
Normotonics without treatment	15	15.1 ± 3.4
Normotonics treated by sarcolysine	15	10.2 ± 1.6
Hypotonics treated by sarcolysine	15	5.1 ± 0.6*

*The differences are reliable to other groups, $P < 0.05$.

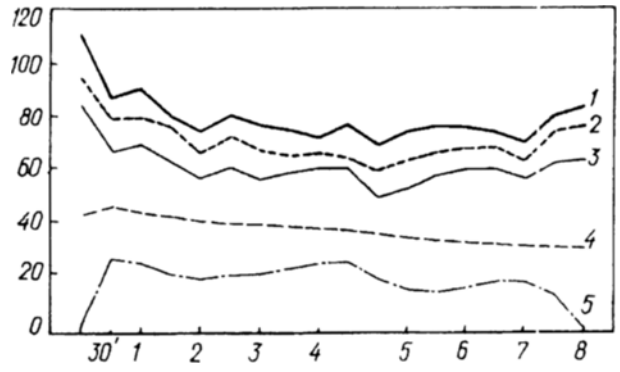

Fig. 1. Dynamics of the main parameters of blood circulation in rats with graft sarcoma during eight-hour intravenous injection of Naniprus: 1) systolic pressure (mm Hg); 2) dynamic-mean pressure; 3) diastolic pressure; 4) pulse rate (beat/min); 5) Naniprus dosage (mkg/100 g/h). Vertically: pressure, mm Hg; ×10, pulse rate, beat/min; ×10, dosage of the preparation, mkg/100 g/h, horizontally: duration of procedure, h.

2. Antitumoral Effect of the Seances of Controlled Medicinal Hypotension. The procedure of controlled arterial hypotension was performed on day 15–16 after hypodermal grafting of Sa-45; it was repeated in a day, i.e., the procedure was performed twice. The reduction of pressure was achieved by intravenous injection of the pharmacological preparation Naniprus (manufactured in Bulgaria), which was injected by an automatic batcher at a rate of 0.5 ml/h in the dose of 250 mkg/100 g/h. A day after the second procedure the animals were not subject to the experiment, and tumors were removed and weighted and histologically examinated.

The results of the observations over the changes in arterial pressure during the seances of hypotension are shown in the figure.

It is seen from the presented data that intravenous injection of Naniprus in the given dose ensures the reduction of intra-arterial pressure, on the average, by 30% from the initial. Both maximal, and mean and minimal pressure reduced practically to the same extent. The frequency of systoles in eight-hour hypotension gradually decreased and by the end of the procedure it was 20% lower than the initial value.

The decrease in the tumor mass was, on average, 45% as compared to the control (6.1 ± 0.8 g and 3.3 ± 0.6 g, respectively, $P < 0.05$). The character of morphological changes developing in tumoral nodules under the effect of two seances of arterial hypotension indicated the leading role of vascular reactions in the total effect of the given procedure.

Thus, the antitumoral effect of repetitive seances of medicinal hypotension and the increase in the effect of sarcolysine in persistent arterial hypotension indicate that the reduction of pressure can be used in clinics as a

fundamentally new approach in treating malignant timours. In contrast to traditional chemotherapy when injected preparations exert a toxico-damaging effect directly on tumoral cells, the reduction of arterial pressure causes, first of all, changes in hemodynamics of a tumoral tissue: the retardation of the growth and the death of malignant cells are the secondary effect resulting from the violation of microcirculation and transcapillary transfer and also from the reduction in the growth of vessels at the periphery of tumors [3]. This fact can be used to overcome numerous medicinal stabilities.

We consider that a new approach to the therapy of malignant tumors can be used along with traditional methods and realized, besides the studied ways, due to the employment of a wide range of hypotensive preparations of various effects, extra- and intravascular surgical interventions directed to the reduction of arterial pressure, changes in rheological properties of a blood flow, etc. Specific definition of these problems requires further experimental and clinical studies.

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