

# EFFECT OF ORGAN SPECIFIC SERA ON THE LOCALIZATION OF METASTASES FROM THE BROWN-PEARCE TUMOR

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It is known that localization of metastases in certain organs and systems is not always explainable on the basis of the anatomical structure of the organs. This problem has interested many investigators for a long time.

We approached its study from an immunological position, keeping in mind the well-known injurious, cytotoxic action of antibodies on the cells of tissues and organs [1,2]. We obtained organ specific sera, which we injected, in varying doses, into rabbits with transplanted Brown-Pearce tumors, in order to injure and sensitize the cells and tissues of specific organs.

## EXPERIMENTAL METHOD AND RESULTS

By separate immunizations of sheep with suspensions of ground tissue from the lungs, liver, kidneys, and Brown-Pearce tumor, we obtained specific sera. The titers of the specific antibodies in the sera, in relation to the antigens from the tissues in the aforementioned organs, were the following: antilung, 1:80; antiliver, 1:80; antikidney, 1:160; antitumor, 1:80 (antibody titer was determined by complement fixation). All the sera reacted with homologous antigens in higher titers than with nonhomologous ones.

The experiment was carried out on 44 male rabbits of the chinchilla family, weighing 2500-3000 g. The animals were divided into 6 groups: 5 groups (according to the number of the sera) of experimental animals (8 in each group), and one control (4 rabbits). Each group of experimental rabbits was subdivided into 2 subgroups of 4 rabbits: each rabbit in one subgroup received the respective serum 9 times in 24 h, using a dose of 2 ml per injection; each rabbit of the other subgroup got 0.2 ml of serum per single injection (0.6-0.7 ml of serum per kg of body weight, 5 times over a period of 3 days). The animals of each group were injected with only one of the sera. The serum injections were begun one day after transplantation of the tumor.

The use of the large doses (2 ml) in frequent and numerous injections was calculated to cause an injurious, cytotoxic action, while the use of small doses (0.2 ml) was designed to produce a stimulatory effect.

Tumor material for the transplant was taken from rabbits, under sterile conditions, on the 20th day after tumor inoculation, and prepared in the form of a suspension of tissue fragments in physiological saline, with a dilution of 1:10. This suspension was injected into the testicle of each rabbit, in a dose of 1 ml. On the 22nd day after the tumor inoculation, all the animals were sacrificed.

In order to determine the degree to which the organs were metastatically involved, a count was undertaken according to the following method. We counted the number of metastases on the surface of the organ, and in serial sections of the organ, approximately 5 mm in thickness. In the heavily infiltrated organs, we counted the number of metastases in a small piece of determined weight, and then calculated the number on the basis of the weight of the whole organ. The degree of involvement of the testicles and epiploon with tumor growth was determined from their weight.

Table 1 shows the average number of metastases found in each of the counted organs of the animal, according to groups.

The data presented in Table 1 show that in the rabbits that were injected with the large dose of antiliver serum the number of metastases in the liver was 4.8 times greater than in the control, 12 times greater than with injection

TABLE 1. Degree of Metastasis of a Brown-Pearce Tumor to the Lungs, Liver, and Kidneys of Rabbits Injected with Organ Specific, Antitumor, and Normal Sera (Average Number of Metastases)

Sera	Investigated organ	Serum dose		Control (serum not injected)
		2 ml. 9 times	0.2 ml. 5 times	
		aver. no. of metastases		
Antilung	Lungs	—	—	3.7
Antiliver	Liver	24	2	5
Antikidney	Kidneys	40.7	—	0.5
Antitumor	Lungs	—	1	3.7
	Liver	0.6	14.6	5
	Kidneys	1	16	0.5
Normal	Lungs	11.6	14	3.7
	Liver	15.3	20.3	5
	Kidneys	0.3	7	0.5

TABLE 2. Degree of Metastasis of a Brown-Pearce Tumor to the Lungs, Liver, and Kidneys of Rabbits Injected with Organ .

Sera	Investigated organ	Serum dose		Control (serum not injected)
		2 ml, 15 times	0.2 ml, 5 times	
		aver. no. of metastases		
Antilung	Lungs	1.7	—	—
Antiliver	Liver	50.1	19.2	29.7
Antikidney	Kidneys	24.5	2.5	10.5
Normal	Lungs	0.2	14.2	—
	Liver	22	40.2	29.7
	Kidneys	17.5	18.5	10.5

ried out by the same method as in the first experiment. On the 24th day after inoculation, all the animals were sacrificed. The number of metastases in the organs of each group were counted according to the method described above. The results of the experiment are presented in Table 2.

Table 2 shows that with injection of antiliver serum in large doses, the number of metastases in the liver was 26 times greater than with injection of small doses, 16.8 times greater than in the control, and 22.7 times greater than with injection of large doses of normal serum. With injection of antikidney serum in large doses, the number of metastases in the kidneys was 9.8 times greater than with small doses, 2.3 times greater than in the control, and 1.4 times greater than with injection of large doses of normal serum. The injection of normal serum produced different results.

The results obtained are evidence that an immunological reaction apparently takes part in the processes of metastasis, and that localization of metastases is related to the sensitizing effect of antibodies on cells.

It may be postulated that the formation in tumors of autoantibodies foreign to the organism, connected with the conversion of normal cells into malignant ones, causes the organism to respond with defense reactions, including the formation of antibodies. The defense function served in the first stages of the disease by the formed autoantibodies seems to be replaced by a cytotoxic effect. The cytotoxic action of the antibodies leads to injury and sensitization of the cells in individual organs, resulting in the formation of a favorable soil for the fixation and survival

of the small doses, and 1.5 times greater than with injection of large doses of normal serum. With use of large doses of antikidney serum, the number of metastases in the kidneys was 80 times greater than in the control, and 4.9 times greater than with injection of large doses of normal serum. With injection of small doses of antikidney serum, metastases were not observed in the kidneys at all.

With injection of normal sheep serum, we could not establish any regular pattern in the localization of metastases. With injection of both small and large doses of normal serum, the number of metastases was almost the same.

In order to verify the data obtained, a second experiment was set up.

In this, we used 4 sheep sera: antilung (titer 1:80), antiliver (1:40), antikidney (1:160), and normal. Aqueous-saline extracts from tissues of the corresponding organs of the rabbit (liver, kidneys, lungs) served as the antigens for immunization of the sheep.

In the experiment, 36 male rabbits were used, divided into 5 groups; 4 groups of experimental animals, with 8 rabbits per group, and one group of 4 control rabbits. Each group of experimental animals was divided into 2 subgroups (4 rabbits each). The rabbits of one subgroup in each group received one organ specific serum 15 times, in a dose of 2 ml, over an interval of one day. Rabbits of the other subgroup received 0.2 ml 5 times, over a period of 3 days. Injection of serum in a dose of 2 ml began 10 days before tumor inoculation. Serum in the 0.2-ml dose was injected beginning with the third day after the tumor was inoculated.

Tumor inoculation to all the animals was car-

of tumor cells circulating in the blood and lymph. In a number of cases, this apparently causes the localization of metastases associated with malignant neoplasms.

#### SUMMARY

In administration of organospecific sera to rabbits with an inoculated Brown-Pearce tumor, the authors observed a preponderant localization of metastases in those organs to which the antiorganic serum had been administered. A conclusion was drawn on the participation of immunological reactions in the metastatic processes.

#### LITERATURE CITED

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2. J. W. Steiner and R. Volpe, *Canad. Med. Assoc. J.*, 84, 21, 22-23 (1961).

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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 this issue.

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