THE GROWTH OF A PRIMARY TUMOR (SARCOMA M-1) DURING THE TRAINING OF RATS TO HYPOXIA IN THE LOW PRESSURE CHAMBER

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The detection of conditions which enhance the resistance of the animal body to malignant growths and study of the mechanism governing the defensive and compensatory reactions which take place during that process are undoubtedly of great importance for the solution of problems connected with the pathogenesis of tumors.

In addition to immunological investigations, to which in recent years considerable attention has been paid, investigations should also be continued with regard to the influence exerted by unspecific resistance upon the tumorous process.

It is well known that exposure of the animal body to certain stimuli leads to an increased resistance, not only to the stimulus in question, but also to other factors.

For example, animals adapted to the stimulus of cold (hypothermia) proved to be resistant, not only to cold, but also to oxygen deficiency due to various causes [5,6].

Animals which had been trained to conditions of low barometric pressure acquired an increased resistance to the effects of rarefied atmosphere as well as to hypothermia [4].

Training to hypoxia, however, sometimes produces resistance of the animal body in what seems to be quite unexpected directions: e.g., training of animals to hypoxia increased their resistance to irradiation with x-rays [1].

From this point of view studies concerning the influence of training to hypoxia upon the tumorous growth seem to be of certain interest. This question arose also on the basis of certain preliminary results obtained in our laboratory by V. N. Popov.

It was the aim of the present experiments to study the influence of adaptation of rats to hypoxia in conditions of low barometric pressure upon the growth of primary rat tumors (M-1 sarcoma).

METHOD

In our experiments the primary tumor was implanted under the skin of the left thigh (inoculation of 0.2 ml of a 25% tumor tissue suspension in normal saline). The training in the low pressure chamber was performed by keeping the rats daily in the chamber. The training was begun simultaneously with the implantation of the tumor and continued for 10-14 days. The "height" changed depending on the experimental conditions between 6000 m over sea level (353 mm Hg: "soft" training) and 10,750 m over sea level (175 mm Hg: "hard" training). The exposure of the rats to the "height" in question was continued for 50-60 min.

RESULTS

Our findings concerning the relation between the tumorous growth and the training conditions are summed up in the table.

The Influence of Training Conditions in the Low Pressure Chamber upon the Growth of a Primary Tumor (M-1 Sarcoma)

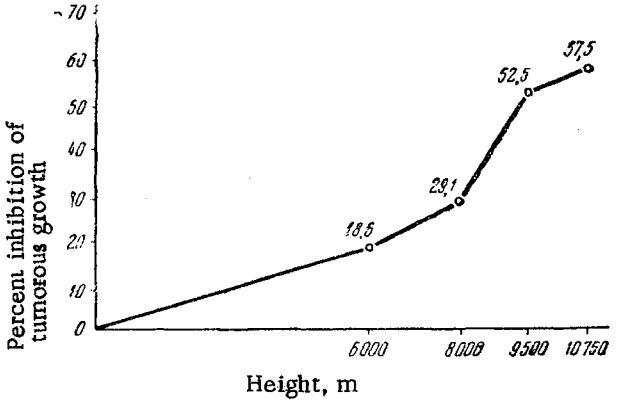
Expt. No.	"Height," m								
	8 000—10 750			6 000			control rats (not trained)		
	no. of rats	average tumor weight, g	no. of rats failing to develop tumor	no. of rats	average tumor weight, g	no. of rats failing to develop tumor	no. of rats	average tumor weight, g	no. of rats failing to develop tumor
1	20	5,11	2	20	6,59	0	10	9,3	0
2	22	3,65	2	22	6,32	1	22	7,7	0
3	15	4,37	0	15	8,99	1	15	10,3	0
Summarized data	57	$M_1 \pm m_1 = 4,37 \pm 0,58$*	4	57	$M_2 \pm m_2 = 7,3 \pm 0,73$†	47	$M_3 \pm m_3 = 9,1 \pm 0,22$		

*Significance of the difference $M_3 - M_1$: $t = 9.8$, $P = 0.001$.
†Significance of the difference $M_3 - M_2$: $t = 2.6$, $P = 0.01$.

The table shows that training of rats in the low pressure chamber inhibits the growth of the tumor and that the "hard" training 8000-10,750 m "over sea level" causes a more marked inhibition. Thus, in the control rats the average weight of the tumor was equal to 9.1 g in all three experiments, but in the rats exposed to " hard " training the average weight of the tumor was only 4.37 g, i. e., less than half as much. The average weight of the tumor in rats exposed to "soft" training (6000 m) was equal to 7.3 g.

The cases in which the tumor failed to develop are of certain interest for the evaluation of the effect exerted by the training of rats in the low pressure chamber upon the growth of the tumor. Among 57 rats trained under "hard" conditions of hypoxia the tumor failed to develop in four rats, and among a similar number of rats trained under "soft" conditions of hypoxia the tumor failed to develop in two cases, whereas in the control group the tumor developed in all 57 rats.

Depending on the experimental conditions, the "height" at which the training was performed was different for various groups of experimental animals and was equal to 6000, 8000, 9500 and 10,750 m, respectively. If we investigate the findings concerning the growth of the tumor in the same order, a not less convincing picture of inhibition of the tumorous growth depending on the "height" of training can be obtained (see figure).



Relation between the inhibition of the tumorous growth and the "height" of rise in the low pressure chamber.

The percent of inhibition of the tumorous growth was calculated by the formula:

$$\frac{C_c - C_e}{C_c} \times 100,$$

in which C_c represents the average weight in the control group and C_e the average weight of the tumor in the experimental group.

The figure shows that the percent of inhibition of the tumorous growth increased parallel to the "height" of training.

The development of the mechanisms which inhibit the tumorous growth has proved to be directly related to the "height" at which the training to hypoxia was performed.

The adaptation to hypoxia is a very complex process. This process involves a number of compensatory mechanisms: changes in respiration and circulation, mobilization of carbohydrate stores, adaptative changes in the metabolism, the number of working capillaries in the brain increases, and so on. As the adaptation advances those compensatory mechanisms which are aimed at an improved utilization of oxygen by the tissues acquire predominant importance [7].

A certain group within the above(far from complete) enumeration of the mechanisms which secure the adaptation of the animal body to lack of oxygen, which adaptation develops during the training to hypoxia, exerts an inhibitory effect upon the growth of the primary tumor.

Studies of the biological nature of these mechanisms, which apparently belong to the mechanisms of unspecific resistance, seems to be of great interest for the clinical oncologist. The search for adequate methods of acting upon an individual affected by a malignant tumor with the aim of stimulating these mechanisms and consequently of developing the unspecific resistance is definitely important.

Recent studies on the influence exerted by repeated exposure of animals to conditions of hypoxia were met with considerable interest. In 1959 an article devoted to that problem was published by G. G. Korobkov [2]. This work is of certain interest, but regrettably the author failed to mention the number of experimental animals and the significance of the results obtained; it is consequently difficult to judge his conclusions.

The present paper thus briefly reports the fact that training of rats in low pressure chambers exerts an inhibitory influence upon tumorous growth. Our findings warrant the conclusion that the inhibitory effect upon the tumorous growth is the more marked, the harder the conditions of training in the low pressure chamber. The development of the mechanisms which inhibit the growth of M-1 sarcoma directly depends on the degree of training to hypoxia to which the rats are subjected.

SUMMARY

The effect of hypoxic training of rats on the growth of transplantable tumors (sarcoma M-1) was studied in experiments involving 161 animals. In training the rats at an "altitude" of 6,000 m, the tumor growth was delayed by 18.6 per cent. With the rise of the training "altitude" there is a progressively increasing development of the tumor growth-inhibiting mechanisms. At the maximal "altitude" of training (10,750 m) the tumor growth inhibition reached 57.5%.

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