CARCINOGENIC EFFECT OF A CARCINOGEN ADMINISTERED REPEATEDLY TO ANIMALS WITH INDUCED TUMORS

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UDC 616-006.04-02:615.7"756"

Many experimental and clinical observations have shown that the animal organism possesses a definite resistance to the onset and development of malignant neoplasms. It has also been found that when a tumor grows in the human body, the resistance of the host to malignant tumors, introduced by either auto- or homotransplantation, is modified [9,11,12]. It may be supposed that in the process of development of a tumor induced by a chemical carcinogen, the resistance of the organism to the carcinogenic action of the chemical agent is also modified.

The object of the present investigation was to study the carcinogenic effect of a carcinogenic agent administered repeatedly to animals at different stages of development of a tumor induced by the same carcinogen.

A fairly extensive literature relating to the study of the action of carcinogenic substances administered successively with different time intervals between the first and second administration [7,8,10] and to the study of the action of the same carcinogenic substance administered simultaneously or at different times by different routes or in different parts of the body [1-6,10] exists. However, no information could be discovered in the literature relevant to the study of the action of a carcinogen on animals in which a tumor induced by the same carcinogen was developing.

EXPERIMENTAL METHOD

Experiments were carried out on female albino rats weighing (at the beginning of the experiment) 90-100 g. The first tumors were induced by injecting 9,10-dimethyl-1,2-benzanthracene (DMBA) subcutaneously into the left thigh in a dose of 0.6 mg in 0.2 ml peach oil; when this dose was injected, a sarcoma developed in 30-50% of the animals. Five or six months after the first injection of the carcinogen, the rats were subdivided into three groups. Group 1 included the animals in which the tumor at this time was the size of a pea. In the rats of group 2, tumors of the same size were removed by surgical excision. Group 3 included animals in which no tumors had appeared by the 5th month after the first injection of the carcinogen. DMBA was injected subcutaneously into the right thigh of the rats of all three groups in the same dose as at the first injection. The rats of group 4 were controls: intact rats of the same weight received an injection of DMBA subcutaneously into the right thigh in the same dose as the animals of the first three groups.

The experiments of series II were conducted in the same manner as those of the preceding series, but DMBA was injected again 10-12 months after the first injection. The tumors in the animals (of the 1st and 2nd groups) of this series which appeared after the first injection of the carcinogen were rather bigger (the size of a plum) than those observed in the rats in the experiments of series I.

EXPERIMENTAL RESULTS

Comparison of the results of the experiments of series I and II shoed that, in the course of growth of the tumor in the animal body, the reactivity of the animal to the repeated action of the carcinogenic substance was modified. The results obtained indicated that this modification of the reactivity of the organism could be subdivided into two stages.

The first stage lasted 5-6 months, and during it the second injection of the carcinogen did not give the same effect as the first. Formation of a tumor at the site of the second injection of DMBA was observed only in occasional cases or was absent altogether (Table 1).

The second and subsequent period was clearly apparent in the 10th-12th month after the first injection of the carcinogen. The second injection of the carcinogen in this period caused the more rapid appearance of a tumor.

Laboratory of Experimental Pathology, Institute of Normal and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Active Member of the Academy of Medical Sciences of the USSR V. V. Parin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 62, No. 8, pp. 86-88, August, 1966. Original article submitted June 7, 1965.

TABLE 1. Development of a Tumor after a Second Injection of a Carcinogen 5-6 Months after the First Injection

Group of animals	Number of animals		Time of appearance of tumor
	total	with a tumor at the site of injection of DMBA	
Rats with a tumor	8	1	8th week
Rats in which the tumor was removed 9 days before reinjection	10	0	–
Intact rats of the same weight (control)	20	11	23rd week

TABLE 2. Development of a Tumor after a Second Injection of a Carcinogen 10-12 Months after the First Injection

Group of animals	Number of animals		Time of appearance of tumor
	total	with a tumor at the site of injection of DMBA	
Rats with a tumor	12	6	8th week
Rats in which the tumor was removed 9 days before reinjection	11	8	8th week
Intact rats of the same weight (control)	20	11	18th week

A tumor appeared at the site of the second injection twice as fast as after the first injection of the carcinogen in the control animals (Table 2). In both the first and the second periods, the change in the reactivity was unconnected with the presence or absence of a tumor at the moment of the second injection of the carcinogen; the effect from the second injection of the carcinogen was identical quantitatively and almost identical qualitatively whether the tumor was still there or whether it had been removed.

Consequently, the decisive factor in the modification of the reactivity of the organism toward the second injection of the carcinogen was not the influence of the tumor at that particular moment, but the changes arising in the organism in the process of growth of the tumor.

Nothing is known of the nature of the mechanisms lying at the basis of the changes in the reactivity of rats to the repeated administration of a carcinogenic agent when a tumor had been present for a long time: it is uncertain whether this action is exhibited against the action of the carcinogen itself or against the subsequent stage of the formation and development of the tumor. It is still not clear whether this modification is specific in character, i.e., whether the change in the reactivity of the organism toward the repeated action of a carcinogenic agent is selective in relation to that particular carcinogen.

LITERATURE CITED

1. S. I. Lebedinskii, in the book: The Problem of Reactivity in Pathology [in Russian], Moscow (1954), p. 322.
2. I. P. Tereshchenko, Vopr. Onkol., 4, 70 (1960).
3. I. Hieger, Am. J. Cancer, 28, 522 (1936).
4. W. G. Jaffe, Cancer Res., 7, 113 (1947).
5. W. G. Jaffe, Cancer Res., 7, 529 (1947).
6. P. S. Lavik, P. R. Moore, H. P. Rusch, et al., Cancer Res., 2, 189 (1942).
7. R. J. Meechan, D. E. McCafferty, and R. S. Jones, Cancer Res., 13, 802 (1953).
8. E. C. Miller, J. A. Miller, and R. R. Brown, Cancer Res., 12, 282 (1952).
9. A. Ravina, Presse med., 65, 1341 (1957).

10. H. L. Richardson, A. R. Stier, and E. Borsos-Nachtnebel, Presse med., 65, 356 (1957).
11. Ch. M. Southam, A. E. Moore, and C. P. Rhoads, Science, 125, 158 (1957).
12. Ch. M. Southam and A. Brunschwig, Cancer, 14, 971 (1961).