EFFECT OF PYROGENAL-INDUCED PYREXIA ON GROWTH OF BROWN-PEARCE CARCINOMA

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UDC 616-006-092.9-09:615.832.8

Injections of pyrogenal (10 injections at intervals of 1 day) before inoculation of the tumor reduce the number of successful takes of Brown-Pearce carcinoma in rabbits from 60 to 25%. Both the pyrexial reaction and activation of the connective tissue are considered to play a role in this effect.

Emphasis has frequently been laid on the inhibitory effect of acute febrile reactions on the growth and development of malginant neoplasma [2-8, 12]. However, individual species of tumors have been shown to differ in their sensitivity to heat [9].

In the investigation described below the effect of fever artificially induced by injection of pyrogenal on growth of the Brown-Pearce rabbit carcinoma was studied.

EXPERIMENTAL METHOD

Sixty chinchilla rabbits of different weights and sexes of which 40 were experimental animals and 20 controls, were used. The tumors were produced by inoculation with 1 ml of a 20% suspension of Brown-Pearce carcinoma, the material being injected into the testis in males and into the subcutaneous cellular tissue of the lateral surface of the right thigh in females. Depending on the times of injection of the pyrogenal, the experimental animals were divided into 2 equal groups (20 rabbits in each group). The animals of group 1 received pyrogenal as 10 injections starting from the 6th-7th day after inoculation of the tumor, while those of group 2 received the pyrogenal injections before inoculation. The rabbits of each group, in turn, were divided into subgroups (with 10 animals in each). In subgroup 1 the pyrogenal was injected in a dose of 100 MPD (minimal pyrogenic doses) daily for 10 days. In subgroup 2 the pyrogenal was injected in the same doses, but on alternate days, i.e., over a period of 20 days. The effects of pyrogenal were assessed from 2 principal criteria: the temperature response and the leukocyte picture of the blood. The intensity of growth of the tumor was determined macroscopically and by calculation of the area of the tumor nodule during the period of observation of the animals, and after their death by histological study of the viscera.

EXPERIMENTAL RESULTS

When pyrogenal was injected in a dose of 100 MPD the rise of the rabbits' body temperature, measured in the rectum by a type ÉTU-M electrothermometer differed before and 2 h after the injection. The greatest amplitude of temperature fluctuations was observed in the animals of group 2, especially in subgroup 2. Characteristically after 3-5 injections of pyrogenal the amplitude of the fluctuations of temperature in the rabbits of all subgroups was slightly reduced, but it soon returned to normal.

The leukocyte response was less definite in character. In contrast to the expected development of leukopenia followed by leukocytosis under the influence of pyrogenal, in some experiments the leukopenia which developed 2 h after the first injection of pyrogenal persisted for a long time and was not followed by

Department of Pathophysiology, A. Aliev Azerbaijan Postgraduate Medical Institute, Ministry of Health of the USSR, Baku. (Presented by Academician of the Academy of Medical Sciences of the USSR P. N. Veselkin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 73, No. 4, pp. 82-85, April, 1972. Original article submitted April 6, 1970.

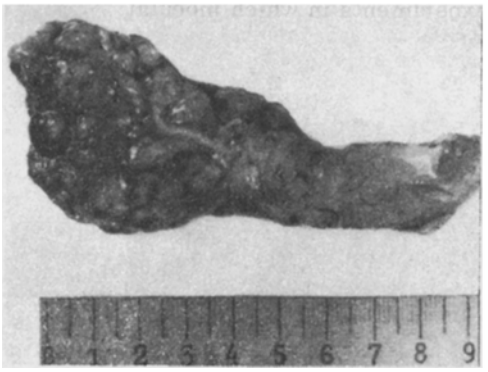

Fig. 1

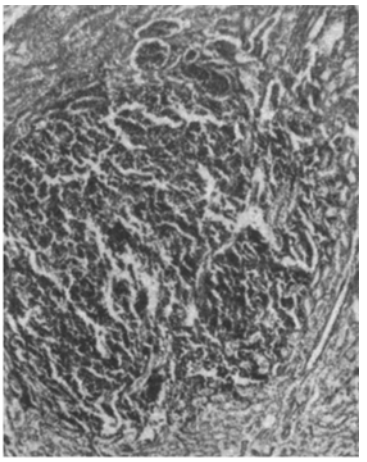

Fig. 2

Fig. 1. Scrotum of rabbit No. 26 dying 19 days after inoculation of tumor. Entire scrotum is covered with metastases.

Fig. 2. Large metastatic tumor nodule in kidney of the same rabbit. Tumor cells are large in size, round or oval in shape, and have hyperchromic nuclei. Cloudy swelling of the epithelium of the convoluted tubules can be seen in the surrounding kidney tissue, 56 ×.

TABLE 1. Results of Inoculation with Brown-Pearce Rabbit Carcinoma Together with Pyrogenal Administration

Group of animals	Subgroup	Tot. number of animals		Animals success. inoc.						no. of animals with absorbed tumors		no. of animals unsuccessfully inoculated	
				tot. no.		no. with isolated tumor		no. with metastases					
		abs	%	abs	%	abs	%	abs	%	abs	%	abs	%
1	1	10	100	5	50	2	40	3	60	2	20	3	30
	2	10	100	6	60	—	—	6	100	1	10	3	30
	Control	10	100	6	60	1	17	5	83	—	—	4	40
2	1	10	100	6	60	2	33	4	67	—	—	4	40
	2	8*	100	2	25	1	50	1	50	—	—	6	75
	Control	10	100	6	60	3	50	3	50	—	—	4	40

*Two rabbits died before inoculation of tumor.

leukocytosis. The investigations showed that of the 20 experimental rabbits of group 1 (7 males and 13 females; 3 males and 7 females in subgroup 1, 4 males and 6 females in subgroup 2), the tumor was successfully transplanted into 11 animals (55%; 5 males and 6 females). The tumor nodules varied in size.

In all cases intratesticular inoculation of the tumor into male rabbits was followed by widespread, generalized metastasization both in the viscera (kidneys, liver, lungs, heart, urinary bladder, intestine) and in the lymph glands, diaphragm, parietal peritoneum, omentum, and mesentery (Figs. 1 and 2).

The intensity of tumor growth varied depending on the methods and duration of pyrogenal therapy (Table 1). Among the animals of subgroup 1, which received pyrogenal daily, 50% of the rabbits developed the tumor although generalized metastasization was observed in only 1 male rabbit. Among the animals of subgroup 2, in which the administration of pyrogenal was prolonged, growth of the tumor was observed in 60% of rabbits and in all these cases the intensity of metastasization was extremely high.

In the rabbits of the control subgroup (4 males and 6 females) the proportion of successful takes was similar to that in the animals of experimental subgroup 2, with a mean value of 60%; in the males it was 100% whereas in the females it did not exceed 33%.

The results were quite different in the next series of experiments in which inoculation of the tumor was preceded by injection of pyrogenal. The results of these experiments showed that the febrile state, if produced and maintained for a long period of time, in some cases created a very unfavorable background for tumor transplantation. Of a total of 20 rabbits in group 2 (9 males and 11 females), inoculation was successful in only 8 animals (40%; 3 males and 5 females).

Among the rabbits of subgroup 1 (daily injections of pyrogenal) the percentage of successful inoculation of the Brown-Pearce tumor was much higher (60) than among the previous animals. Growth of the tumor was most commonly accompanied by marked metastasization, especially in the kidney, liver, lungs, and lymph glands.

Analysis of the results thus shows that the growth and development of Brown-Pearce carcinoma took place less intensively in animals receiving pyrogenal than in the rabbits of the control group. This applies especially to the experimental animals which received a course of 10 injections of pyrogenal on alternate days before inoculation of the tumor. The results concur to some extent with clinical observations [5, 7, 9-11] in which comparisons of the histories of patients with cancer and other diseases have shown that the morbidity from cancer was much less in persons with a past history of acute inflammatory diseases than of other diseases.

The writers consider that the unfavorable action of pyrexial reactions on the growth of tumors is based on a number of different causes, but the decisive role is evidently played both by local effects of pyrexia and activation of the functions of the connective-tissue system, with particular emphasis on a marked increase in the intensity of oxidation. This interpretation appears to be well grounded because earlier experiments [1, 2] showed that pyrogenal induces a sharp increase in the intensity of oxidative processes and, in particular, of porphyrin metabolism in rabbits with Brown-Pearce carcinoma, and porphyrins are known to be the chief component of many glycolytic enzymes and to play a catalytic role in tissue respiration.

Besides inhibition of tumor growth in rabbits, another factor which should be noted is the slight increase in the duration of survival of the animals receiving pyrogenal, although this was accompanied by a more rapid loss of weight than took place in the control animals.

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