

SOME ASPECTS OF RECURRENCE AND METASTASIZATION OF EHRLICH'S CARCINOMA

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The phenomenon of inhibition of growth of smaller tumor nodes during the development of a neoplasm was described as early as in 1906, and was subsequently called concomitant immunity [1, 4]. It is suggested that during growth of a tumor in vivo the host organism is sensitized to tumor cells, and for that reason their subsequent transplantation into the same host leads to destruction of the transplant [2]. The process of suppression of growth of the secondary tumor node by the primary is strictly antigen-specific. For instance, after transplantation of sarcoma S-10 into animals with this tumor, total suppression of growth of the secondary transplant was observed, whereas the primary node of sarcoma S-10 did not affect growth of sarcoma S-11 [3]. On the other hand, we know that after surgical removal of a tumor node growth of metastases is activated, i.e., the already sensitized host organism does not arrest the development of secondary tumors [6].

This contradiction was the reason for the present investigation, whose aim was to study the effect of surgical removal of an intramuscularly growing Ehrlich's carcinoma on the development of recurrences and metastases and on growth of a secondary transplant of this tumor.

EXPERIMENTAL METHOD

Experiments were carried out on male (CBA \times C57BL/6) F_1 hybrid mice aged 2-3 months. An Ehrlich's carcinoma was transplanted into the thigh muscle in a dose of $1 \cdot 10^6$ cells. The tumor node was removed under ether anesthesia on the 29th day after transplantation of tumor cells. The tumor in some animals was not removed, and subsequent transplantation of tumor cells took place into the healthy limb. On the 3rd, 10th, and 17th days after the operation, $1 \cdot 10^4$ Ehrlich's carcinoma cells were transplanted intramuscularly into the animals. In a parallel series the same number of cells was injected into intact mice, and into the opposite limb of animals with a tumor that was not removed and was still growing. Each experiment was repeated at least three times. The criteria of evaluation of the results were determination of the mean duration of survival of the animals and the size of the tumor on the 7th and 14th days after transplantation. Ten mice were used in each group. Statistical analysis of the data was carried out by the Fisher-Student method. Differences were considered to be significant at the $p \leq 0.05$ level.

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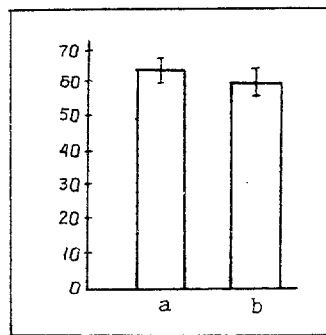


Fig. 1. Effect of surgical removal of tumor node of intramuscularly growing Ehrlich's carcinoma on mean survival time of mice. Abscissa, experimental groups: a) animals not treated surgically; b) animals treated surgically. Ordinate, days after transplantation of tumor.

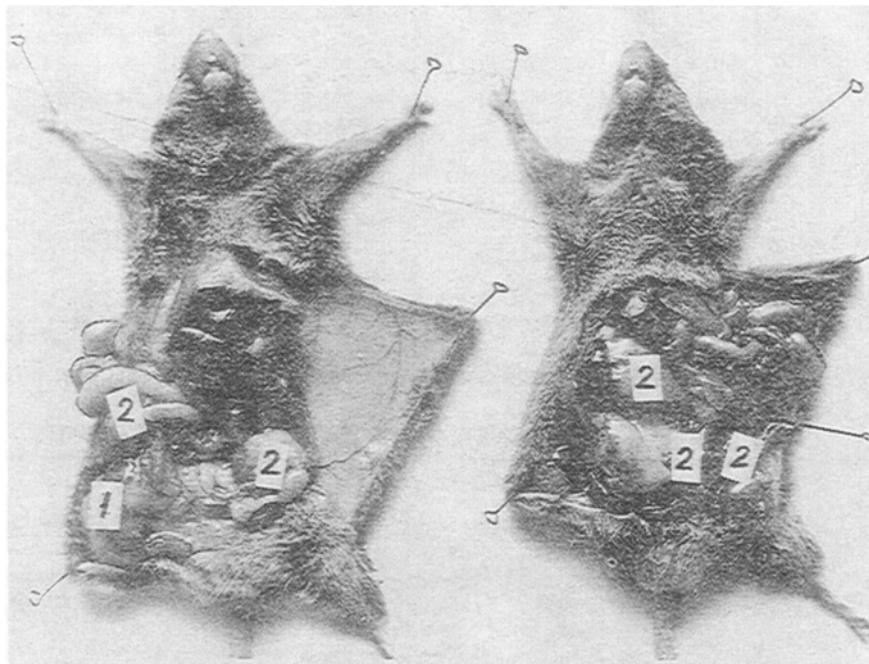


Fig. 2. Recurrences and metastases of Ehrlich's carcinoma after surgical removal of primary node: 1) recurrence; 2) metastases in peritoneal cavity.

EXPERIMENTAL RESULTS

The results of a study of the effect of surgical removal of the tumor node on survival of mice with transplanted Ehrlich's carcinoma are given in Fig. 1. They show that the mean duration of survival of the animals not undergoing operation was 62.2 days compared with 59.4 days in those treated surgically, i.e., removal of the tumor did not lead to lengthening of survival of the mice. In mice not treated surgically, the tumor was observed to invade the peritoneal cavity, but the development of metastases was not recorded in a single animal of this group. In the

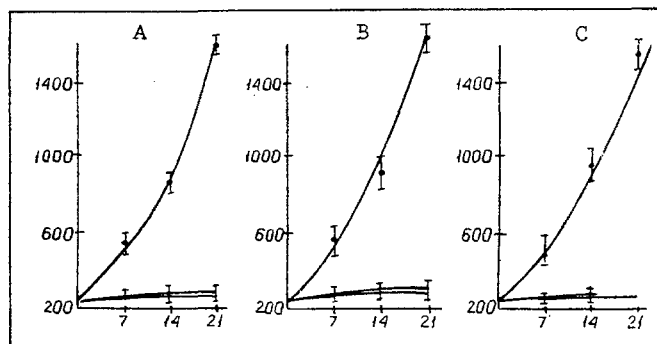


Fig. 3. Dynamics of growth of secondary transplant of Ehrlich's carcinoma. Abscissa, days after transplantation of secondary graft; ordinate, volume of thigh muscle, conventional units. A: 1) Animals with growing tumor (32nd day after transplantation); 2) animals after removal of tumor (32nd day after transplantation and 3rd day after operation); 3) intact animals. B: 1) Animals with growing tumor (39th day after transplantation); 2) animals after removal of tumor (39th day after transplantation and 10th day after operation); 3) intact animals. In groups 1 and 2, death of animals was noted, starting with the 40th day after transplantation of primary tumor. C: 1) Animals with growing tumor (46th day after transplantation); 2) animals after removal of tumor (46th day after transplantation and 17th day after operation); 3) intact animals. Death of animals was noted in groups 1 and 2, starting with 40th day after transplantation of primary tumor.

surgically treated mice, recurrences occurred in 40-60% of cases, and independently of this process, metastases developed in all the animals in the abdominal lymph nodes and spleen (Fig. 2). Growth of metastases in the subcutaneous cellular tissue was observed in 20-30% of cases.

Data showing the dynamics of growth of a transplanted Ehrlich's carcinoma in intact animals, in surgically treated animals on the 3rd day after removal of the tumor, and in mice with the same tumor but growing (32nd day after transplantation), are given in Fig. 3A. They show that in the control group of animals progressive growth of the Ehrlich's carcinoma was observed after transplantation of $1 \cdot 10^3$ tumor cells into the thigh muscle. At the same time growth of this tumor after secondary inoculation of tumor cells was not observed in the animals of groups 2 and 3. Similar results were obtained after transplantation of the same number of Ehrlich's carcinoma cells on the 7th and 17th days after removal of the tumor (Fig. 3B, C).

The results thus show that the mean duration of survival of mice treated and not treated by surgical removal of the tumor was virtually the same. It can be postulated that this parameter is independent of the number of tumor cells removed. A similar situation is observed, probably, during treatment of animals with a tumor by cytostatics: although inhibition of tumor-growth is recorded, there is no increase in the duration of survival of the treated animals compared with the control group [5]. Repeated transplantation of tumor cells into mice with a growing Ehrlich's carcinoma and into animals treated by surgical removal of the tumor does not lead to the development of a new tumor node, whereas in animals not previously in contact with this tumor, it was observed to develop. These results are in full agreement with our previous findings, when growth of a tumor was inhibited after secondary transplantation [2, 3]. It must be pointed out, however, that inhibition of growth of the transplant in animals undergoing the operation was observed against the background of rapid development of metastases. During the experiment their diameter in the peritoneal cavity increased to 2 cm. This selective inhibition of growth of transplanted tumor

cells, accompanied by rapid development of metastases, cannot be explained by a difference in their antigenic determinants, for growth of metastases was not observed in animals not treated surgically. Consequently, the primary tumor and metastases have a sufficient number of common antigenic determinants to ensure that the primary tumor node inhibited growth of metastases in animals not treated surgically. It can be tentatively suggested that the development of metastases depends not only on the properties and particular features of the tumor cells, but it is an active process, controlled by the body as a whole. This may also explain the absence of any increase in the mean duration of survival of animals after removal of the tumor compared with mice not treated surgically, despite elimination of a large number of tumor cells. In our opinion, this hypothesis requires further intensive study.

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