The Effects of a Transplanted Granulosa-Cell Tumor on Mice in Parabiosis*

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Growth of a transplanted granulosa-cell tumor in mice is associated with an increased blood volume and sinusoidal dilatation in the liver, spleen, and adrenal glands (4, 5, 8, 9, 10). The effect is not related to the estrogenic activity of the tumor (1, 6). In order to study the mechanism underlying these changes, parabiotic mice were used—one partner having a transplanted granulosa-cell tumor.

METHODS

Twelve pairs of parabiotic mice were studied. Fragments of a granulosa-cell tumor (18 C57) were transplanted into adult animals of the C57 black strain. This tumor originally arose in a castrated animal of the C57 strain that had a homologous transplant of an ovary into the pancreas (11); it is now in its fifth transfer generation. During the first and second transfer generation, mice given a preparation containing progesterone had an increased frequency of growth of the tumor. The tumor requires no extrinsic hormonal supplement.

The transplants were made subcutaneously using a #15 gauge trocar. As soon as a small nodule was palpable at the site of the transplant, the animal was united in parabiosis to a nontumor-bearing litter-mate. The technic used was that of Sauerbruch and Heyde (13), as modified by Bünster and Meyer (3).

Eleven of the twelve pairs of mice were castrated 5-7 days before being united in parabiosis, and vaginal smears were made at intervals during the course of the experiment. All animals were kept on a standard diet and water ad libitum.

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An unrefined concentrate containing approximately 200-250 lU. progesterone/cc; obtained from the Glidden Company through the courtesy of A. E. Engstrom.

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OBSERVATIONS

Nontumor-bearing animals were in parabiotic union with tumor-bearing animals from 11 to 110 days before either dying or being sacrificed. Following parabiosis, only those animals that gained weight and showed a normal amount of activity were studied.

At autopsy the animals with tumors had enlarged livers and spleens (Table 1). Grossly, the adrenal glands of these animals were enlarged and congested, and the hearts were dilated but had not increased in weight. None of these changes were observed in the nontumor-bearing partners. Vaginal smears of the castrate tumor-bearing females with large tumors indicated the presence of an estrogenic substance, while the smears of the castrate nontumor-bearing parabionts were all of a diestrous type.

Histological examination of the livers of animals with tumors revealed sinusoidal dilatation varying from slight to extreme dilatation, with isolated cords of liver cells between large dilated sinuses. No sinusoidal dilatation was observed in the livers of the nontumor-bearing partners (Figs. 1 and 2).

The spleens of the tumor-bearing animals showed greater vascular engorgement than the spleens of the nontumor parabionts. There was also dilatation of the sinusoids at the cortico-medullary junction of the adrenal glands of the tumor-bearing animals (Figs. 3 and 4).

The uteri of the castrate tumor females were enlarged and showed the effects of estrogenic stimulation, while the uteri of the castrate nontumor-bearing female partners were small and showed the typical changes of castration (Figs. 5 and 6).

DISCUSSION

In this series, animals with tumors weighing 1 gm. or more had sinusoidal dilatation in the liver, spleen, and adrenal glands, yet these changes were not observed in the nontumor-bearing partners united in parabiosis.
While blood volume studies were not performed in this experiment, the sinusoidal dilatation in the tumor animals was secondary to an increased blood volume (9). The observation that the nontumor-bearing parabiont does not develop any of the hypervolemic effects when united in parabiosis to an animal bearing a granulosa-cell tumor for periods up to 110 days may be due to the fact that the agent responsible for the hypervolemia is not produced in sufficient concentration to cross over to the normal animal, or it may be inactivated more efficiently by the normal animal. The possibility of a concomitant infection associated with this tumor as an explanation of the hypervolemic changes does not seem tenable, as the presence of vascular anastomoses between parabiotic animals has been demonstrated. When the dye, brilliant red, is injected intravenously into one parabiotic rat, it is present in equal concentrations in both animals in about 6 hours (12); and rat erythrocytes injected intravenously into one parabiotic mouse are present in the blood of the nontreated partner in 20 minutes, and large numbers are present 120 minutes after the injection (7). If the hypervolemic effects were due to an infectious agent of the nature of a virus associated with this tumor, then it is likely that these effects would occur in the nontumor-bearing partner.

The estrogenic substance produced by the tumor is in quantities too small to cross over into the normal animal, or it is quickly inactivated, for its effects are not observed in the nontumor-bearing parabiont. When estradiol is injected into one parabiotic rat, the concentration of estradiol must be increased approximately 40 times before its effects will be observed in a parabiont twin (2).

**SUMMARY**

1. C57 mice, when united in parabiosis for periods up to 110 days to litter-mates bearing a transplanted granulosa-cell tumor, do not develop the hypervolemic effects seen in the tumor-bearing animals.

2. It is unlikely that the hypervolemia associated with mice bearing a granulosa-cell tumor is due to an infectious agent.

3. The estrogenic-like substance produced by a transplanted granulosa-cell tumor in one mouse of a parabiotic pair is not sufficient to stimulate a castrate parabiont twin.

**REFERENCES**


Fig. 1.—Section of liver of tumor-bearing animal No. 80 C57 showing sinusoidal dilatation. Mag., 32 mm. objective and 8 X ocular.

Fig. 2.—Section of liver of nontumor-bearing animal No. 39 C57 parabiosed to No. 80 C57 for 54 days. Mag., 32 mm. objective and 8 X ocular.

Fig. 3.—Section of adrenal gland of tumor-bearing animal No. 80 C57. Mag., 32 mm. objective and 8 X ocular.

Fig. 4.—Section of adrenal gland of nontumor-bearing animal No. 39 C57. Mag., 32 mm. objective and 8 X ocular.

Fig. 5.—Section of uterus of tumor-bearing castrate animal No. 80 C57. Mag., 32 mm. objective and 8 X ocular.

Fig. 6.—Section of uterus of nontumor-bearing castrate animal No. 39 C57. Mag., 32 mm. objective and 8 X ocular.
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