Metastasis from the Brain*

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SUMMARY

The present investigation was undertaken to determine whether the failure of brain tumors to metastasize was related to local conditions at the site of origin. Three hamster tumors and two rabbit tumors, known to be capable of metastasis, were transplanted to the brains of animals of the same species. The tumors grew rapidly but killed the bearers before sufficient time had elapsed to allow the formation of metastatic growths. Accordingly, tissues of the tumor-bearing animals were transplanted homologously to normal adult animals to provide additional time for contained tumor cells, if present, to manifest themselves by growth. Tumor growth occurred in tissue transplants in all five instances, and it was concluded that conditions peculiar to the brain were not operative in the failure of brain tumors to metastasize.

Although occasional instances of metastasis from malignant tumors of the brain have been reported in the literature, this diagnosis is not widely accepted, and the lesions described as metastatic are generally thought to be co-existing primary growths of other tumors (4, 5). The absence of metastasis is usually considered to be causally associated with conditions distinguishing the brain from other bodily sites of growth such as the blood-brain barrier, the absence of lymphatic vessels, or the anatomical structure of cerebral veins. In view of the local invasiveness of the tumors, their anaplastic appearance, and capacity to survive heterologous transfer, the possibility that the failure to metastasize relates to factors resident in the tumors themselves rather than in the site of origin has received less attention.

Experimental animal tumors transplanted to the brain kill rapidly, and microscopic examination shows no evidence of dissemination. However, the course of the tumors in the brain is of shorter duration than that required for the production of metastasis from transplants in other bodily regions, and, even in the event of blood stream dissemination, the presence of detectable secondary growths could not be expected. The present paper describes the results of experiments designed to provide a longer period of time for tumor cells, if present in the tissues of animals bearing brain transplants, to manifest their presence. To this end, such tissues were transplanted homologously to normal animals, and these animals were observed to determine whether tumor growth occurred in their transplants.

MATERIALS AND METHODS

Three hamster tumors, consisting of a melanotic melanoma, an amelanotic melanoma, and a lymphoblastic lymphoma, and two rabbit tumors, the Brown-Pearce carcinoma and the V-2 carcinoma, were used in these experiments. Brain transfer was accomplished through a small drill hole in the right parietal region, and fragments of tumor measuring approximately 1 mm. in diameter were deposited deep in the cerebral substance by means of a trocar.

The animals were kept under close observation and were killed when signs of increased intracranial pressure became evident. The brains were examined for meningeal extension, and only animals with tumors localized in the brain substances were used for the experiment. The organs to be tested were removed by sterile technic, and fragments of tissue were dissected from scattered areas of their substance for transfer. Fragments from hamster organs measuring approximately 2 mm. in diameter were transplanted subcutaneously in the axillary region of normal, untreated, adult hamsters, and rabbit organ fragments measuring about 1 mm. in diameter were transplanted to the anterior chamber of normal, untreated, adult rabbit eyes.

As a rule, four to six hamsters were employed in each hamster organ test and two rabbits in each rabbit organ test. The hamsters were stock animals obtained from a local breeder, and weighed between 75 and 100 gm. The majority of rabbits were pure bred Dutch, but occasionally animals of Himalayan or standard English breed were used. No attempt was made to select donors and recipients of the same stock.

The animals bearing organ transplants were examined at frequent intervals to determine the presence or absence of tumor growth in their transplants, and all transplants were subjected to histological study.

RESULTS

Before describing the results obtained in these experiments, some discussion of the methods employed is in
TABLE 1

THE INCIDENCE OF TUMOR GROWTH IN HOMOLOGOUS SUB-CUTANEOUS TRANSPLANTS OF TISSUE FROM HAMSTERS BEARING TRANSPLANTED TUMOR IN THEIR BRAINS

<table>
<thead>
<tr>
<th>Tumor-Bearing Hosts</th>
<th>Recipients of Tissue from Tumor-Bearing Hosts</th>
<th>Lung</th>
<th>Systemic Blood</th>
<th>Liver</th>
<th>Spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>Residence in brain (days)</td>
<td>No. hams*</td>
<td>No. with tumors</td>
<td>No. hams*</td>
<td>No. with tumors</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>12</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Amelanotic melanoma</td>
<td></td>
<td>12</td>
<td>23</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>25</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Melanotic melanoma</td>
<td></td>
<td>13</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>4</td>
<td>2</td>
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<td></td>
<td></td>
<td>21</td>
<td>16</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

* No. hams* used as recipients of tissue from tumor-bearing hosts.
† No. recipients bearing tumors derived from transplanted tissue.

order, especially since the technic is based on the capability of adult tissue to survive homologous transplantation. Other experiments by this technic have been successfully carried out in this laboratory (1, 2), and it has been observed that small fragments of adult tissue of the size employed will survive homologous transfer for long periods of time, particularly in the rabbit and the hamster.

In the present experiments the transplanted adult tissue survived for a sufficient period of time to provide a nidus for the growth of the contained tumor cells. Transplants in the hamsters' subcutaneous space remain barely palpable until such growth occurs. However, earlier histological sections show vascularization with preservation of structure, and during the latter part of the quiescent period small foci of tumor growth may be found. The tumor rapidly invades the remainder of the transplant and extends into adjacent tissues to form a readily palpable nodule of progressively increasing size resembling in all respects the mass produced by a tumor transplant itself. The transplants of adult rabbit tissue in the anterior chamber show little change for several weeks but remain pink in color, and their vascularization is obvious to the naked eye. Foci of tumor growth may be found on microscopic examination before increase in the size of the transplant occurs, but the presence of tumor is made apparent between the 19th and 25th days by the sudden occurrence of rapid growth with eventual filling of the chamber and corneal rupture (Figs. 1–8).

Hamster tumors.—The three hamster tumors have been carried by serial transfer in this laboratory for many years, and their behavior has been the subject of special study. It should be noted in the present context that, on subcutaneous transfer, vascular invasion with the appearance of tumor cells in the lung occurs on the 6th day in the case of the lymphoma, on the 8th day in the case of the amelanotic melanoma, and is delayed until the 5th week in the case of the melanotic melanoma. The three tumors

![Fig. 1.](image1.png) Homologous anterior chamber transplant of normal adult rabbit lung 32 days after transfer. Note preservation of architecture with survival of alveoli and bronchioles. Pigmented tissue on right is iris. Mag. X30.

![Fig. 2.](image2.png) Homologous anterior chamber transplant of lung. The donor of the lung was a rabbit bearing a brain growth of the V-2 tumor, and the recipient was killed 22 days after transfer. Note expanded alveoli, enlarged bronchioles, and dense area of fibrosis containing nests of proliferating V-2 tumor cells. Mag. X25.

![Fig. 3.](image3.png) Similar transplant removed 30 days after transfer. Tumor growth has completely replaced the transplanted lung tissue. Mag. X20.

![Fig. 4.](image4.png) Higher-power view of section shown in Figure 2. Bronchial elements are surrounded by growing tumor cells. Mag. X225.

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FIG. 2.—Homologous anterior chamber transplant of lung. The donor of the lung was a rabbit bearing a brain growth of the V-2 tumor, and the recipient was killed 22 days after transfer. Note expanded alveoli, enlarged bronchioles, and dense area of fibrosis containing nests of proliferating V-2 tumor cells. Mag. X25.

FIG. 3.—Similar transplant removed 30 days after transfer. Tumor growth has completely replaced the transplanted lung tissue. Mag. X20.

FIG. 4.—Higher-power view of section shown in Figure 2. Bronchial elements are surrounded by growing tumor cells. Mag. X225.
Figs. 5, 6, 7.—Lung tissue from other rabbits bearing brain growths of the V-2 tumor 23, 25, and 26 days after transfer to the anterior chambers of normal rabbits' eyes. Mag. X200, 225, and 200.

Fig. 8.—Homologous anterior chamber transplant of lung. The donor of the lung was a rabbit bearing a brain growth of the Brown-Pearce tumor, and the recipient was killed 19 days after transfer. Mag. X200.
grow in all animals on brain transfer, and microscopic study of extracranial organs fails to show metastatic foci of growth or recognizable tumor cells.

It is apparent from Table 1, however, that tumor cells are present in these tissues, since, in each instance, homologous transplants become the site of tumor growth.

The lymphoma grows rapidly in the brain, and the majority of animals die between the 6th and 8th days after transfer. Tumor cells are present in transplants of lung, systemic blood, liver, and spleen during this period, and it is clear that the cells of the lymphoma do invade cerebral veins and are disseminated throughout the body.

This is also true of the cells of the amelanotic and melanoctic melanomas. Tumor cells are present in the lungs of animals with brain growths of the amelanotic melanoma on the 12th and 14th days, and 80 per cent of their transplants are tumor-bearing. The melanotic melanoma grows more slowly than the other tumors of this series, and some of the animals survive until the 21st day. Tumor cells are present in the lung as early as the 13th day, and, inasmuch as the cells are transported to this organ by the venous circulation, it must be assumed that vascular invasions precede this date. This length of period contrasts with the 7-week interval required for vascular invasion from the subcutaneous space, suggesting that the anatomical structure of the cerebral veins or some other factor operative in the brain actually functions to promote rather than to hinder vascular invasion.

Rabbit tumors.—The Brown-Pearce and the V-2 are both epidermoid carcinomas of the skin but show many differences in behavior, including speed of vascular invasion. Anterior chamber transplants of the Brown-Pearce tumor invade blood vessels on the 7th day after transfer, whereas similar transplants of the V-2 tumor require 19 days of growth before vascular dissemination occurs. On brain transfer the Brown-Pearce grows more rapidly than does the V-2, and animals die within 15 days, whereas rabbits bearing the V-2 may survive until the 21st day. In neither case is this period of time adequate for the production of metastasis of sufficient size to be detected by either gross or microscopic examination, and thorough study of histological sections of lung stained by ordinary techniques fails to show the presence of recognizable tumor cells. Nevertheless, tumor cells are present in this organ and manifest themselves by growth when the life of the tissues is prolonged by transfer to normal animals (Table 2).

It is apparent from this table that the cells of both tumors invade cerebral vessels and lodge in the lung. Brown-Pearce tumor cells are present in the lung from the first determinations made on the 13th day, and it is obvious that invasion of cerebral vessels precedes this date. Tumor cells are not present in transplants of lung from bearers of the V-2 tumor at this time but appear on the 18th day, marking the occurrence of vascular invasion of this tumor from the brain as identical with that from the anterior chamber.

**DISCUSSION**

The results of these experiments are evidence that the failure of brain tumors to metastasize is not related to local factors pertaining to the brain as a site of growth. In fact, the data suggest that vascular invasion is actually more readily effected in the brain than in other bodily regions. The failure to metastasize in the present instances is due to the short life of the animal bearing the brain transplant, and the formation of metastatic growths in homologous tissue transplants is delayed for some weeks after the animal's death.

It is obvious that the failure of human glioblastomas and medulloblastomas to metastasize is not due to the short life of the patients bearing them, because such individuals may live for many months after biopsy proves the tumor to be heterotransplantable and, therefore, presumably metastasizable. Apparently such tumors do invade vascular walls, since their cells have been detected in peripheral blood (3). The possibilities exist that such cells may not be capable of endothelial binding and permeation or that they lack the capacity to evoke stroma from the interstitial tissues of the body. It is suggestive in relation to the latter point that human glioblastomas will survive heterotransplantation only in the anterior chamber of the eye and in the brain itself, whereas other human tumors can be successfully transplanted to other bodily regions after a generation in the eye or brain of a heterologous host. In any case, the problem is open to experiment, and pertinent investigation is in progress.

It is a point of interest that tumor growth occurs in such a high proportion of lung transplants. The largest fragments were 2 mm. in diameter and were selected at random, and the fact that the majority contained tumor cells suggests that tumor cells are present diffusely in very high numbers throughout the organ. It should be emphasized that the tumor cells are bound in the lung and that the results are not a reflection of the blood content of the fragment. Identical results are obtained with perfused lungs, and, in the majority of cases, the tumor-bearing animals employed have been bled to death, and the tissues used for transfer are anemic in appearance and bloodless.

**REFERENCES**


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