ABSTRACT
This study reports an easily accomplished and reliable model of metastatic tumor in the brains of mice. Five experimental groups of female C3H/Bi mice received left intracardiac injections of a syngeneic KHT sarcoma cell suspension (1 × 10^6 cells) and were followed until death. Two groups of mice also received 3000 mads of radiation to a limited cardiac port 24 hr after tumor injections. All mice were completely autopsied, and the brains were examined both grossly and microscopically. Metastatic brain tumor developed in 60 to 70% of mice; the tumor foci were parenchymal, usually multifocal, and had wide distribution throughout the cerebrum, brainstem, and cerebellum. There was occasional meningeal tumor, but tumor never involved the skull, choroid plexus, pituitary gland, or local extracranial structures. Cardiac irradiation did not increase the number or the mean survival of mice with metastatic brain tumor but did decrease the total tumor burden of individual animals by markedly reducing the incidence of metastatic lung tumor and totally preventing tumor infiltration of the heart. This demonstration of consistently produced blood-borne metastatic brain tumor in mice should provide a valuable research model which will allow the central nervous system to be studied for internal mechanisms and/or external factors which influence the arrest and growth of embolic tumor cells in the brain.

INTRODUCTION
Although it is estimated that 18% of patients with systemic cancer have metastatic brain tumors at autopsy (1, 29) and evidence is accumulating that there is an increased incidence of cerebral metastasis in patients who with treatment survive primary disease (14, 28), virtually nothing is known about factors or mechanisms within the brain which allow or prevent neoplastic growth. This area of research has been severely hampered by the lack of appropriate and reliable small animal models of primary and metastatic brain tumors.

A number of murine brain tumor models have been developed for testing chemotherapeutic agents, but most of these involve direct inoculation of the brain either with tumor fragments (2, 15, 33), tumor cell suspensions (8, 28, 38-40), or virus particles (30, 32, 41). Thus, tumor develops only after an initial violation of the integrity of cerebral substance and the "blood-brain barrier"; these models provide no information about conditions necessary for the implantation and growth of blood-borne metastatic disease.

A more physiological brain tumor model involves the use of the nitrosoureas which successfully induce significant numbers of developmental brain tumors in rats (11, 18, 21). Although the rat provides an interesting animal model for some types of studies, the mouse has been the primary animal used to define the cellular, genetic, and immunological factors affecting tumors. Unfortunately, compared to the rat, the mouse brain is much more sensitive to the carcinogenic effects of nitrosoureas, and the incidence of intracerebral tumor in mice remains low despite considerable research effort directed at establishing a reliable model with a high yield of neurogenic tumors (10, 31, 34, 35, 37).

Two recent studies report models of metastatic brain tumor produced by the direct injection of tumor cell suspensions into the carotid arteries of rats (20, 36). Significant technical problems which had to be circumvented before a meaningful number of intracerebral parenchymal tumor metastases developed were reported in both studies. Direct carotid artery injection in mice is technically quite difficult, but recent reports by Nicolson et al. (25, 26) suggested that left i.c. injections of B16 melanoma tumor cells would produce brain metastases in mice. In the present study, we describe a technique of direct left i.c. injection which is easily accomplished and when used to inject KHT sarcoma cells in syngeneic C3H mice reliably produces multiple blood-borne parenchymal tumors in the brain.

MATERIALS AND METHODS

Mice. Female C3H/Bi mice were used for all experiments and were obtained either from Simonsen Laboratories, Gilroy, Calif., or from Microbiological Associates, Bethesda, Md. Mice weighed 18 to 22 g at the beginning of each experiment, and for each experiment all mice used were from the same supplier.

Tumor. The KHT mouse sarcoma was kindly supplied by Dr. J. M. Brown, Stanford, Calif. and was maintained in our laboratory by serial s.c. transplantation every 2 to 3 weeks. This tumor arose spontaneously in a C3H mouse and in this host is very weakly antigenic (19). Single cell suspensions for all injections were made from solid s.c. tumors. Tumors were removed aseptically, being careful to exclude tissue from the surrounding tumor capsule and to discard necrotic tumor tissue. The tumor fragments were placed in Ca^2+- and Mg^2+-free Hanks' balanced salt solution, minced finely with scissors, and were exposed to 0.025% trypsin diluted with Ca^2+ and Mg^2+-free Hanks' balanced salt solution for 15 min while being stirred constantly. The resulting suspension was passed through sterile glass wool and centrifuged at 4° at 1200 rpm for 15 min. The cells were washed once

1 This research was supported by the Veterans Administration MRIS 1534 Grant IN-320 from the American Cancer Society and NIH Grant 5507 RR 5353-16.

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and resuspended in Hanks' balanced salt solution with antibiotics (penicillin 100 units/ml, streptomycin 100 μg/ml). Cell viability was assessed by trypan blue exclusion (85 to 90% viable) and the viable cell count adjusted to a concentration of $5 \times 10^6$ cells/ml. Because single cell suspensions were always made from s.c. tumors, some host cells were undoubtedly included each time cell suspensions were made; no effort was made to quantitate or identify these cells.

**I.C. Injecting Devices.** Cardiac injecting devices were made using 10 cm of clear polyethylene tubing with an internal diameter of 0.015 inch and an outer diameter of 0.043 inch (Tubing No. 7405, Clay Adams, Division of Becton, Dickenson and Co., Parsippany, N. J. 07054). With a small file, 7 mm of the sharp end of a 27-gauge disposable needle were detached, and the blunt end of this piece was inserted into one end of the tubing for a distance of 3 mm, allowing 4 mm of needle to project. An intact but blunted 27-gauge needle was inserted into the other end of the tubing, and a tuberculin syringe holding the tumor cell suspension was attached to its hub. Meticulous care was taken to assure removal of all air from the device.

**Left I.C. Injection Technique.** Mice were anesthetized with inhalation methoxyflurane (Pitman Moore, Inc., Washington Crossing, N. J.). As we maintained anesthesia with a nose cone, the mice were restrained, the anterior chest wall was cleansed with alcohol, and a midline skin incision was made over the upper chest cage exposing the clavicle and upper ribs. The second intercostal space was identified, and the injecting needle was quickly inserted to its entire depth of 4 mm; the needle was directed towards the midline, starting 2 mm to the left of the sternum and was angled 45° relative to the chest wall. Successful needle insertion into the left heart resulted in a pulsatile flow of bright red blood into the transparent tubing of the injecting device. If there was no blood return or if dark blood with minimal pulsation was obtained, the needle was withdrawn and after assuring its patency was reinserted. Once accurately positioned, the needle was manually held while a second individual slowly injected a total volume of 0.2 ml (1 × $10^6$ cells) of tumor cell suspension. Successful injections were accomplished without detection of any resistance to flow by the person handling the syringe; if resistance was encountered during the course of an injection that animal was discarded. Upon completion of an injection, there was often but not always return of pulsatile blood flow into the tubing of the injecting unit. The skin incision was closed with a single surgical clip, and all animals were returned to standard conditions of care.

**Cardiac Irradiation.** Cardiac irradiation was given 24 hr after i.c. tumor injection. Mice were anesthetized with sodium pentobarbital (67.5 mg/kg i.p.) and placed in a lead-shielded jig which allowed for exposure of an anterior cardiac port. The radiation port did not include the upper portion of the thymus gland. Radiation was delivered as a single fraction of 3000 rads at a focal skin distance of 44 cm. A 0.01-mm aluminum, 0.25-mm copper filter created a half-value layer of 1.3 mm copper, and a dose rate of 100 rads/min was delivered using 250 kV at 15 ma.

**Evaluation of Tumor.** Mice were observed twice daily until death or the development of a morbid state, at which time they were sacrificed. An autopsy was performed on every mouse as soon after death as possible. The brains from all mice were placed in 10% buffered formalin, and the remainder of the body was examined carefully for evidence of gross tumor. All hearts from Experiments 1 and 2 (Tables 1 and 2), a few hearts from Experiments 4 and 5, and representative lung and other tissue specimens from all experiments were also placed in 10% buffered formalin. Following fixation, the brain from each mouse was hand cut into 3 sections, and these plus the other fixed tissue were processed for routine light microscopy and examined histologically after staining with hematoxylin and eosin. Except for the brain, determination of whether an organ was involved with tumor was made on the basis of gross observation, scoring only tumor presence or absence. Brain involvement was also scored as tumor either being present or absent, using both gross and microscopic examination. Statistical comparisons of tumor data from nonirradiated and irradiated groups of mice were made with the $\chi^2$ test.

### Table 1
Anatomic location of metastatic tumor produced by left i.c. injections of KHT tumor cells

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Cardiac irradiation</th>
<th>No. of mice</th>
<th>No. with brain tumor</th>
<th>No. with heart tumor</th>
<th>No. with lung tumor</th>
<th>No. with tumor elsewhere$^b$</th>
<th>No. with brain tumor only</th>
<th>No. with single anatomic tumor focus</th>
<th>No. with 2 anatomic tumor foci</th>
<th>No. with 3 or more anatomic tumor foci</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>10</td>
<td>7 (70)$^a$</td>
<td>8 (80)</td>
<td>6 (60)</td>
<td>5 (50)</td>
<td>0</td>
<td>0</td>
<td>4 (40)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>8</td>
<td>5 (62.5)</td>
<td>8 (100)</td>
<td>6 (75)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>3 (37.5)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>22</td>
<td>16 (72.7)</td>
<td>18 (81.8)</td>
<td>14 (63.6)</td>
<td>5 (22.7)</td>
<td>0</td>
<td>2 (9)</td>
<td>10 (45.4)</td>
<td>10 (45.4)</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>11</td>
<td>7 (63.6)</td>
<td>0</td>
<td>3 (27.3)</td>
<td>7 (63.6)</td>
<td>2 (18)</td>
<td>4 (36.3)</td>
<td>1 (9)</td>
<td>5 (45.4)</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>7</td>
<td>4 (57.1)</td>
<td>0</td>
<td>3 (42.8)</td>
<td>1 (14.3)</td>
<td>3 (42.8)</td>
<td>5 (71.4)</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>1 + 2 + 3</td>
<td>No</td>
<td>40</td>
<td>28 (70)$^a$</td>
<td>34 (85)</td>
<td>26 (65)</td>
<td>11 (27.5)</td>
<td>0</td>
<td>3 (7.5)</td>
<td>17 (42.5)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>4 + 5</td>
<td>Yes</td>
<td>18</td>
<td>11 (61.1)</td>
<td>0</td>
<td>6 (33)</td>
<td>8 (44.4)</td>
<td>5 (27.8)</td>
<td>9 (50)</td>
<td>1 (5.6)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>$p$: 1, 2, 3 vs 4, 5</td>
<td>NS$^c$</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.02</td>
<td>NS</td>
<td>NAG</td>
<td>NAG</td>
</tr>
</tbody>
</table>

$^a$ Liver, adrenal, ovary, and soft tissue.

$^b$ Numbers in parentheses, percentage of mice with tumors.

$^c$ NS, not significant.
RESULTS

Clinical. Mice tolerated i.c. injections remarkably well. Approximately 5% of mice died within min following injection and an occasional mouse died in the first 24 to 48 hr; none of these early mortalities was included in the analysis of results. Mice with tumor usually became symptomatic 12 to 24 hr before they died and exhibited roughened fur, paucity of movement, and a hunched posture. In addition, when the brain was involved with tumor, mice circled, had marked postural imbalance, and seizures. Mice with extensive lung disease exhibited obvious respiratory distress. Cardiac irradiation resulted in complete fur loss, both anteriorly and posteriorly, over an area which corresponded to the radiation port. Mice which received cardiac irradiation in the absence of tumor suffered loss of fur but no other ill effects and were all alive at the termination of experiments. All mice had gross evidence of thymic tissue at the time of autopsy.

Gross Tumor Locations. Table 1 records the anatomic location of tumor in the 5 experiments performed with this model. In all experiments, 57 to 73% of animals had evidence of tumor metastases in the brain; cardiac irradiation did not increase this incidence of metastatic brain tumor. Nonirradiated animals had a high incidence of extensive involvement of the lungs (60 to 75%) and heart (80 to 100%). In Experiments 4 and 5, the irradiated hearts were totally protected against tumor growth, and radiation significantly reduced the incidence of tumor in the lungs ($p < 0.05$). The lung tumor which was present in animals from these latter experiments usually consisted of only a few isolated tumor nodules. The number of mice with metastatic tumor in other organs (adrenal, ovary, liver, and soft tissues) was quite variable among the experimental groups, and cardiac irradiation did not obviously contribute to either an increase or decrease in the number of metastases to these locations. The incidence of tumor in mice from Experiment 2 is probably low since this experiment was terminated on Day 17 when 4 mice were still living. The number of mice having only a single anatomic focus of tumor was increased by cardiac irradiation ($p < 0.001$) and 5 of 18 (27.8%) mice (Experiments 4 and 5) so treated died with brain tumor only ($p < 0.01$).

Survival Data. Table 2 and Chart 1 present survival data. A consistent mean survival time of 15 days was observed in Experiments 1 and 3. Cardiac irradiation delayed the onset of mortality as well as increased the median survival time. However, when only those mice which had evidence of brain tumor are considered differences in survival times between groups were not significant (Chart 2). There were no tumor-free survivors among the nonirradiated mice; in contrast, one mouse in each of Experiments 4 and 5 survived without evidence of tumor anywhere when the experiments were terminated on Day 34.

Metastatic Brain Tumor, Gross and Microscopic. Although most metastatic tumors were multifocal, 2 mice dying after Day 21 had single tumor masses in the brain. In all mice, neoplastic deposits were parenchymal and were found in all parts of the cerebral hemispheres, the midbrain, lower brainstem, and cerebellum. Occasionally, tumor was present in the meninges over a cerebral convexity, and although some tumor deposits abutted on the ependymal lining of the ventricles, tumor never involved the choroid plexus. Tumor also never involved the skull, pituitary gland, or the cranial nerves at the base of the brain. In all but one case, tumor was grossly apparent either at the time a brain was removed or when it was sectioned.

KHT tumor deposits in the brain formed loosely arranged, rounded deposits of clumps and fingers of neoplastic cells; these tumor foci caused no appreciable inflammatory response but were almost always associated with local hemorrhage (Fig. 1). The tendency for tumor to hemorrhage increased with tumor size, and some tumor foci were obliterated and replaced by large areas of hemorrhage. Although the most common neoplastic pattern consisted of variably sized discrete parenchymal tumor foci (Fig. 2), an occasional brain showed perivascular tumor spread with extensive tumor filling Virchow-Robin spaces. The tumor

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>No. of mice</th>
<th>Cardiac irradiation</th>
<th>Day of first death</th>
<th>No. mice alive at experiment termination</th>
<th>Survival (days)</th>
<th>Day of last mouse with brain tumor died</th>
<th>Survival of mice with brain tumor (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>No</td>
<td>12</td>
<td>22</td>
<td>0</td>
<td>15.3 ± 3.13d</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>No</td>
<td>12</td>
<td>17</td>
<td>4</td>
<td>15.6 ± 4.25</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>No</td>
<td>9</td>
<td>25</td>
<td>0</td>
<td>22.6 ± 6.64</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Yes</td>
<td>15</td>
<td>34</td>
<td>1</td>
<td>22.9 ± 8.45</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>Yes</td>
<td>14</td>
<td>34</td>
<td>1</td>
<td>22.9 ± 8.45</td>
<td>23</td>
</tr>
</tbody>
</table>

* Times are in relation to date of tumor injection which was Day 0.
* $p < 0.001$ when Experiments 1 + 3 are compared to Experiments 4 + 5.
* $p < 0.2$ when Experiments 1 + 3 are compared to Experiments 4 + 5.
* Mean ± S.D.
* Not applicable; experiment was terminated on Day 17.

Student's t test, and the 4-fold $\chi^2$ test, comparing survivals above the overall median, were used to analyze the survival data.
cells were homogeneous with distinct cytoplasmic boundaries and had large, darkly staining nuclei with very prominent clumped chromatin. Mitotic figures were seen frequently (Fig. 3).

**Histology of Other Organs.** Hearts from nonirradiated mice which contained tumor were easily identified at the time of autopsy. Microscopically, tumor extensively infiltrated the myocardium, separating individual cardiac muscle cells, and grew in clumps at the epicardial and ventricular surfaces. Hearts from mice which had been irradiated but not given injections of tumor were histologically normal when examined 33 days after the single dose of radiation. Tumor-inoculated, irradiated hearts showed no evidence of tumor but did have tiny focal regions of fibrotic scarring with occasional hemosiderin; these scars most likely were the result of damage from the injecting needle and/or from tumor cells which had been killed by radiation.

Depending on the degree of tumor involvement, the histological picture in the lungs ranged from a few well-circumscribed tumor nodules to extensive sheets of neoplasia which obliterated the normal pulmonary architecture. Metastatic tumor to the ovary and adrenal destroyed the target organ, and the tumor mass usually had extensive central necrosis.

**DISCUSSION**

The results reported by this study establish a consistent, easily reproduced model of hematogenous spread of metastatic tumor in the CNS of mice. Once the technique was mastered, tumor injections proceeded rapidly and with attention to detail (removing all air from the injecting unit, assuring needle patency, positively identifying the second intercostal space, and frequent changing of injecting devices), most mice tolerated the procedure without difficulty and exhibited no ill effects until they became symptomatic from tumor growth. Although the addition of cardiac irradiation did not increase the number of mice which developed brain metastases, it did provide a much cleaner model by markedly reducing the total tumor burden of individual animals. Most of the cardiac-irradiated mice which developed brain tumors died with CNS symptomatology rather than from the effects of tumor growth elsewhere.

The lack of extracranial neoplastic disease in our model increases its research value. Extracranial neoplasms occur frequently in brain tumor models involving direct injection of tumor into the brain (38) unless elaborate procedures are used to seal the skull puncture site completely (39). In the model developed by Ushio et al. (36) in which the common carotid artery of rats was given direct injections of Walker 256 tumor cells, there was extensive local extracranial disease even after prior ligation of the external carotid artery. Only by giving cyclophosphamide i.v. were they able to reduce significantly the amount of extracranial tumor. Cyclophosphamide is known to suppress antibody production in mice (17), and it has been suggested that it may interfere with macrophage function (7). Prior work from our laboratory has suggested that macrophages may be involved in nonspecific tumor cytotoxicity within the CNS (8, 9). Thus, any model of metastatic brain tumor which depends on an immunomodulating or cytotoxic agent to provide a significant incidence of metastasis is precluded from use in immunological or chemotherapeutic studies. Because much of our present knowledge of tumor immunology is derived from experiments using mice (27), our mouse model of brain tumor should allow application of that knowledge to study immunological aspects of CNS neoplasia. Peritoneal macrophages from normal and cardiac-irradiated mice showed no difference in function when tested in an *in vitro* cytotoxicity assay used routinely in our laboratory (22), and it seems doubtful that the limited cardiac radiation port which spared thymic tissue would cause significant alteration of the immune system.

None of the cardiac-irradiated mice had obvious physiological cardiac dysfunction. Brown et al. (5) and Leach and Sugiuira (23) demonstrated that the murine heart had remarkable resistance to single-dose radiation (1200 to 5000 rads), and the benign histological appearance of the irradiated hearts from this study would suggest that the mouse

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3 F. K. Conley, unpublished data.
Metastatic Brain Tumor in Mice

heart tolerates a single radiation dose of 3000 rads without difficulty. Likewise, although the spinal cord was directly in the radiation field, our mice had no clinical evidence of cord dysfunction, and Goffinet et al. (16) demonstrated that a single dose of radiation had to be in excess of 3000 rads to produce symptomatic myelitis in C3H mice and that clinical signs of damage only became evident many weeks following the radiation treatment. The mouse spinal cords were not examined microscopically either by Goffinet et al. or in the present study.

The initial work establishing our brain tumor model involved searching for brain metastases following the i.v. injection of cells from various tumor lines into syngeneic hosts. Microscopic examination of the brains of 60 C3H mice 17 days after i.v. inoculation of KHT sarcoma cell suspensions (prepared, as in the present study, by trypsinization of solid s.c. tumors) revealed 2 brains with small microscopic metastatic foci; thus, it was known that KHT sarcoma would infrequently metastasize to the brain. The KHT sarcoma has been used extensively to explore factors involved searching for brain metastases following the i.v. injection of cells from various tumor lines into syngeneic hosts. Microscopic examination of the brains of 60 C3H mice 17 days after i.v. inoculation of KHT sarcoma cell suspensions (prepared, as in the present study, by trypsinization of solid s.c. tumors) revealed 2 brains with small microscopic metastatic foci; thus, it was known that KHT sarcoma would infrequently metastasize to the brain. The KHT sarcoma has been used extensively to explore factors which contribute to metastatic tumor spread (3, 4, 7) since it will spontaneously metastasize from a s.c. location to the lungs; the incidence of spontaneous metastasis to the CNS is unknown. In humans, sarcomas rarely metastasize to the CNS, but Gercovich et al. (14) reported a 36% incidence of metastatic cerebral sarcoma in patients whose primary disease had been stabilized for at least 6 months by chemotherapeutic drugs, and Mehta and Hendrickson (24) reported an 18% incidence of hematogenous CNS metastasis in patients with treated Ewing’s sarcoma. Mechanisms responsible for the late metastatic tumor pattern are not known, but our study using KHT sarcoma in which very few metastatic foci developed in the brain following i.v. injection of tumor would suggest that to produce metastases in the brain the brain must be the initial recipient of a tumor cell bolus and be exposed to large numbers of viable cells. Recent work by Nicolson et al. (25, 26) supports this conclusion, but they also present convincing evidence that certain tumor cells have definite brain affinity similar to the tumor cell affinity for lung which had been demonstrated previously (12, 13). Using a B16 melanoma, Brunson et al. (6) found no brain metastases following i.v. injections of tumor cells but were able to produce a few brain tumors following i.c. injection. By serial in vitro-in vivo selection techniques, these researchers established a B16 melanoma line which would produce brain tumor 100% of the time following i.c. injections, and further cloning produced a cell line which would go to the brain in 100% of animals after tail vein injection of cells. Since with our model we were able to produce a high incidence of multiple brain metastases without prior cell line selection for brain preference, there seems little doubt that, like the selected B16 melanoma line, the KHT sarcoma cell also must possess certain critical characteristics which allow for embolic arrest and subsequent tumor growth in the brain.

Previously, Zeidman and Buss (43) had looked at the vascular beds of lung, liver, and kidney (44) and had demonstrated that morphological characteristics of tumor cells (42) determined the occurrence of embolic arrest in a particular tissue. In the only similar study done in the CNS, Kawaguchi and Nakamura (20) injected tumor cells (Yoshida sarcoma and 6 strains of rat ascites hepatoma) directly into the carotid artery of rats, collected internal jugular venous blood, and found a difference in the transcerebral passage time of tumor cells depending on the type of tumor cell injected. They also demonstrated an inverse relationship between the incidence of subsequent development of intracerebral tumor and the transcerebral passage time of tumor cells. Although their study did not consider the possibility that cell surface differences among the various tumor cell lines were responsible for their results, Brunson et al. (6) have been able to document cell surface differences between their brain- and lung-selected B16 melanoma lines; such differences may account for organ preference by a particular tumor. While our study did not address identification of cellular characteristics or of factors promoting metastasis in the CNS, our model apparently fortuitously satisfied many of the yet undetermined criteria necessary for establishing metastatic brain tumor. Future application of our model to experiments designed to delineate the component parts of the process of metastatic tumor implantation and growth in the brain should increase our understanding of mechanisms of CNS neoplasia.

ACKNOWLEDGMENTS

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REFERENCES


Fig. 1. Coronal section of mouse brain with 3 discrete parenchymal foci of metastatic KHT sarcoma. H & E, × 10.

Fig. 2. Small discrete focus of metastatic KHT sarcoma in the brain of a mouse following left i.c. injection of tumor. H & E, × 120.

Fig. 3. High-magnification photomicrograph of metastatic KHT sarcoma in a mouse brain. Numerous extravascular RBC between tumor cells, and 2 mitotic figures in the lower right corner. H & E, × 630.
Development of a Metastatic Brain Tumor Model in Mice

Frances K. Conley


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