Experimental Brain Tumors, with a Report of Those Induced in Dogs by Rous Sarcoma Virus

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Spontaneous mammalian brain tumors vary greatly in appearance and biological behavior.\textsuperscript{79,130} Because of this lack of uniformity, it is difficult to study their effects upon cerebral function and anatomy and to evaluate procedures for their diagnosis and treatment. Such investigations require reproducible animal tumors with characteristics resembling those of human intracranial lesions.\textsuperscript{63,113} The selection of these tumors and of the hosts in which they grow must be determined by the similarity of the neoplasms to spontaneous human tumors and by the size and availability of the animals.

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A wide variety of neoplasms have been intracranially implanted, and many brain tumors have been transplanted to extracranial locations. Transplanted tumors are unsatisfactory for many experiments because of histologic differences from spontaneous lesions, necrosis, or tissue reactions, even in such "immunologically shielded" locations as the brain. Primary induction of satisfactory tumors would remove many of the problems inherent in transplantation. Intracranial tumors have been primarily induced by radiation (Table 1), chemicals (Table 2), and viruses (Table 3).

The most widely-used agents for such primary induction have been intracranially implanted chemical carcinogens. The aver-

**TABLE 1**

<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Animal</th>
<th>Tumor*</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Gamma rays and neutrons</td>
<td>Mouse</td>
<td>Pituitary</td>
<td>26, 28, 101, 102</td>
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<tr>
<td>Iodine-131 and sodium-24</td>
<td>Mouse</td>
<td>Pituitary</td>
<td>12, 13, 20, 25, 27, 30-33, 37</td>
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<tr>
<td>Thorium</td>
<td>Man</td>
<td>Meningioma</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoma (extracranial)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>&quot;Brain tumor&quot;</td>
<td>99</td>
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<tr>
<td>X-rays</td>
<td>Man</td>
<td>&quot;Central nervous system&quot; (?)</td>
<td>48, 51, 115</td>
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<tr>
<td></td>
<td></td>
<td>Craniohypophyngioma</td>
<td>38</td>
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<tr>
<td></td>
<td></td>
<td>Sarcoma</td>
<td>59, 106</td>
</tr>
<tr>
<td></td>
<td>Monkey</td>
<td>Glioma</td>
<td>45</td>
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<td></td>
<td>Mouse</td>
<td>Pituitary</td>
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<tr>
<td>Rat</td>
<td></td>
<td>Glioma†</td>
<td>76</td>
</tr>
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<td></td>
<td>Meningioma†</td>
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<td></td>
<td>Neurilemmoma (extracranial)†</td>
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<tr>
<td></td>
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<td>Sarcoma (extracranial)†</td>
<td>43</td>
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* Tumors are intracranial unless otherwise specified. Designation is that given by authors. Question mark follows those tumors in which statistical evidence of tumor growth as a result of radiation is doubtful.
† Animals in which these tumors were found may not have been exposed to radiation in each case. Description of experiments is incomplete.
age times required for brain tumor induction in mice and rats using intracranial chemicals are approximately 250 days for gliomas and 290 days for sarcomas. Reports have been made of tumor production in rats in times as short as 32 and 45 days, in scantily described experiments. From 1 to 2½ years were required to produce four brain tumors among 13 dogs in which methylcholanthrene was implanted.

The induction times for intracranial tumors caused by viruses are much shorter than for those caused by chemicals. Polyoma virus has induced meningeal sarcomas in as many as 70% of the hamsters inoculated shortly after birth, frequently in less than 30 days. Simian vacuolating virus (SV40) can produce tumors of the ventricular ependyma or choroid plexus in up to 100% of the hamsters inoculated, but most have not been found until more than 100 days after inoculation. Only three brain tumors induced by adenovirus-12 have been reported, and these were undifferentiated or undistinguishable. Rous sarcoma virus (RSV) has produced intracranial tumors in mice, rats, hamsters, rabbits, guinea pigs, cats, and a variety of fowl, sometimes within 15 days after inoculation.

The Schmidt-Ruppin, Carr-Zilber (Svet-Moldavsky), Mill-Hill (Harris), Bryan “high titer”, and “Standard” strains of RSV have been shown to be oncogenic in mammals. Three RSV strains were used in the experiments reported here, in an attempt to grow brain tumors in dogs. A preliminary report has been made of our experiments using the Schmidt-Ruppin and Bryan “high titer” strains. Dogs were chosen as the experimental hosts because the frequency with which they develop spontaneous brain tumors is similar to that of humans and because of their availability and large size.

Materials and Methods

Seventy-six mongrel dogs from 12 litters were inoculated intracerebrally with cell-

* The “Standard” strain was obtained from Dr. Ray Bryan, of the National Cancer Institute, and has been designated as the CT-559 strain by the Laboratory of Viral Carcinogenesis. This “Standard” strain is presumed to be similar to the original strain of virus isolated by Rous.

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**TABLE 2**

Intracranial and neurogenic tumors induced by chemicals

<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Animal</th>
<th>Tumor*</th>
<th>References</th>
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</thead>
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<tr>
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<td>Mouse</td>
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<td>123, 124, 135</td>
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<td>123, 124, 135</td>
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<td></td>
<td></td>
<td>Pituitary</td>
<td>129</td>
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<tr>
<td></td>
<td></td>
<td>Sarcoma</td>
<td>124, 125</td>
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<td>Sarcoma (?)**</td>
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<td>111</td>
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</table>

* Tumors are intracranial unless otherwise specified. Designation is that given by authors. Question marks follow those tumors which were poorly described or in which the histologic diagnosis is open to doubt.

** Askanyar’s descriptions and interpretations are unclear (see Zimmerman and Arnold). One rabbit in which a tumor was found had received an intracerebral injection of fetal rabbit tissue along with the benzpyrene.
<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Animal</th>
<th>Tumor*</th>
<th>References</th>
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<td>2-FAA and 2,7-FAA‡</td>
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<tr>
<td></td>
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<td>Adamantinoma</td>
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<td>Glioma</td>
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<td>Pituitary</td>
<td>112</td>
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<td>35, 61, 80, 81, 88, 84, 95, 111</td>
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<td>Sarcoma (intracranial and extracranial)</td>
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<td>8-ortho-hydroxyquinoline§</td>
<td>Rat</td>
<td>Glioma</td>
<td>39</td>
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<td>Styrl 430</td>
<td>Rat</td>
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<td>107, 108</td>
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<td>Pituitary</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;Tumor of ependyma&quot;</td>
<td>108</td>
</tr>
</tbody>
</table>

† DMBA refers to 9,10-dimethyl-1,2-benzanthracene.
‡ 2-FAA refers to 2-acetylaminofluorene; 2,7-FAA refers to 2,7-acetylaminofluorene.
§ 8-ortho-hydroxyquinoline is an ingredient in "Contraceptive Cream A," given to rats both orally and vaginally.
free RSV suspension while in utero or shortly after birth. The dogs were divided into four experimental groups: Group 1 contained 18 dogs (two litters) inoculated in utero, Group 2 contained 51 dogs (from 10 litters) inoculated within 48 hours after birth, Group 3 contained four dogs inoculated 8 or 15 days after birth, and Group 4 was a control group containing three dogs inoculated with heat-inactivated virus.

Schmidt-Ruppin (SR), Bryan “high titer” (BHT), and “Standard” (STD) strains of RSV, prepared as previously described, were used for the inoculations. The cell-free virus suspension was injected into the right cerebral hemisphere of each dog (Fig. 1). Those dogs inoculated in utero were injected with 0.2 cc directly through the mother’s uterine wall at laparotomy, while the remaining dogs were inoculated after birth with from 0.35 to 0.6 cc.

Animals dying more than 1 week after injection were autopsied. The brains were fixed and sectioned soon after death and microscopically examined after H. & E. staining. Those dogs which did not die were sacrificed at various intervals up to 93 days after injection.

### TABLE 3

**Intracranial and neurogenic tumors induced by viruses**

<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Animal</th>
<th>Tumor*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus 12</td>
<td>Hamster</td>
<td>“Tumor” (?)</td>
<td>41</td>
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<tr>
<td></td>
<td>Mastomys</td>
<td>“Undifferentiated malignant tumor” (?)</td>
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<td>Polyoma</td>
<td>Hamster</td>
<td>Sarcoma</td>
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<td>Rat</td>
<td>Hemangioma (intracranial and extra-cranial)</td>
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<td></td>
<td></td>
<td>“Skull tumor”</td>
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<td>Rous sarcoma virus (RSV)</td>
<td>Cat</td>
<td>Sarcoma</td>
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<td></td>
<td>Chicken</td>
<td>Sarcoma</td>
<td>89, 90, 103, 105</td>
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<td></td>
<td>Duck</td>
<td>Sarcoma</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>Glioma</td>
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<td></td>
<td>Hamster</td>
<td>Glioma</td>
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<td></td>
<td></td>
<td>Sarcoma</td>
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<td></td>
<td>Mouse</td>
<td>Glioma</td>
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</tr>
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<td></td>
<td>Rabbit</td>
<td>Glioma</td>
<td>66</td>
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<td>Turkey</td>
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<td>Simian vacuolating virus (SV40)</td>
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<td></td>
<td>Rat</td>
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<td>113</td>
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</tbody>
</table>

* Tumors are intracranial unless otherwise specified. Designation is that given by authors. Question marks follow those tumors which were poorly described or in which the histologic diagnosis is open to doubt.
Results and Comments

Group 1. All of the 18 dogs inoculated in utero were either born dead or died within 2 days after birth. None survived more than 5 days after injection and none were autopsied.

Group 2 (Table 4). Twenty-four of the dogs inoculated with active virus within 48 hours after birth survived for more than 1 week and were examined at autopsy. Eighteen dogs (75%) were found to have grossly visible tumor nodules adherent to the dura (Fig. 2), attached to the brain surfaces (Fig. 3), or arising from the ventricular walls (Fig. 4). No tumors were found among the remaining animals in this group upon microscopic examination. Most of the dogs with intracranial tumors, and several without, were found to have dilated ventricles (Fig. 4). No satisfactory explanation for this hydrocephalus was evident in the dogs without tumors.

Group 3. Neither of the two dogs inoculated 8 days after birth was found to have

TABLE 4

Results in dogs inoculated intracerebrally with Rous sarcoma virus (RSV) within 48 hours after birth (See text, Group II)

<table>
<thead>
<tr>
<th>Strain of RSV</th>
<th>Litter number</th>
<th>No. of dogs inoculated</th>
<th>No. of dogs surviving inoculation*</th>
<th>Intracranial tumors present</th>
<th>No intracranial tumors</th>
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<tbody>
<tr>
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<td>SR</td>
<td>BHT</td>
<td>STD</td>
<td>SR</td>
<td>BHT</td>
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<td>4</td>
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<td>4</td>
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<tr>
<td>II</td>
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<tr>
<td>Bryan “high titer” (BHT)</td>
<td>I</td>
<td>3</td>
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<td></td>
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<tr>
<td>VI</td>
<td>6</td>
<td></td>
<td></td>
<td>3</td>
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<tr>
<td>“Standard” (STD)</td>
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<td>VIII</td>
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<td>IX</td>
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<td>16</td>
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<tr>
<td>Totals of all dogs inoculated with active RSV</td>
<td>51</td>
<td></td>
<td></td>
<td>24</td>
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</tbody>
</table>

* Dogs dying within 7 days of inoculation were not routinely autopsied and are therefore not included as having survived inoculation.
brain tumors or hydrocephalus when they were sacrificed 45 days following inoculation. One of the two dogs inoculated when 15 days old died 2 weeks later and was found to have a brain abscess but no intracranial tumors. The other of these two dogs was sacrificed 38 days after inoculation and was found to have both leptomeningeal and periventricular tumors.

Group 4. No abnormalities were found when the three dogs inoculated within 48 hours after birth with heat-inactivated virus were sacrificed at ages 36 or 38 days. The tumors found in Group 2 and Group 3 animals were relatively uniform in both gross and histological appearance, but varied in size. The meningeal nodules could frequently be “shelled out” of the brain but

**Fig. 2.** Sarcoma nodules (arrows) adherent to dura overlying right cerebral hemisphere.

**Fig. 3.** Large sarcoma (arrows) arising from leptomeninges of left frontal lobe.

**Fig. 4.** Pedunculated glioma (arrow) arising from frontal horn of left lateral ventricle. Tumor nodule is 5 mm in diameter. Severe hydrocephalus.
Brain Tumors in Dogs Induced by Rous Sarcoma Virus

Fig. 5. Infiltrating leptomeningeal sarcoma arising from surface of cerebral cortex (arrow) (X6).

Fig. 6. Leptomeningeal sarcoma (X530).

Fig. 7. Sarcoma (left) originating from leptomeninges (small arrows). Subarachnoid space on right (large arrow) (X117).
were microscopically infiltrative (Fig. 5) and were diagnosed as sarcomas (Fig. 6) originating from the leptomeninges (Fig. 7). These infiltrating leptomeningeal sarcomas were found most frequently over the cerebral cortex and along the undersurface of the brain stem, especially near the pituitary and the cerebellum (Fig. 8).

The periventricular tumors usually protruded into the ventricular cavities and were occasionally pedunculated (Figs. 4 and 9). These neoplasms have been diagnosed as Grade 3 astrocytomas or glioblastomas (Fig. 10). Sarcomas and gliomas were usually found in the same animals. It was not uncommon to find 15 or more meningeal tumors over the cortex or invading the brain stem from beneath. Most of the sarcoma nodules were smaller than 5 mm, but a few were 20 mm or more in diameter. Fewer than five gliomas were usually found in a single dog, and almost all were less than 5 mm in diameter.

In several of the Group 2 dogs, subcutaneous scalp nodules were palpable near the site of injection (Fig. 11). These nodules regressed in size and often disappeared completely within 30 to 60 days following injection. Similar subcutaneous nodules, which were histologically diagnosed as fibrosarcomas and which frequently regressed, have been reported following RSV injection in a variety of other animals,\textsuperscript{1,2,4,9,10,11} It is probable that these tumors were caused by virus leakage along the needle track at the time of intracerebral injection.

![Fig. 8. Cross section of cerebellum and brain stem, showing massive sarcoma (arrows) infiltrating ventral surface.](image1)

![Fig. 9. Pedunculated glioma protruding into lateral ventricle (×9).](image2)
Brain Tumors in Dogs Induced by Rous Sarcoma Virus

Approximately half of the dogs in which intracranial tumors were found became cachectic or developed focal neurological signs within 4 weeks after inoculation. The remainder of the animals remained normal in appearance and behavior until their death or sacrifice.

Primary virus-induced brain tumors of the types which we have described are potentially useful in neurological research. The short induction time (average of approximately 35 days), high percentage of tumors (75% in this series), and large size of the hosts (dogs weighing several kilograms at the time of death) fulfill our requirements for a useful experimental intracranial tumor model.

Summary

We have reviewed various techniques for creating experimental intracranial and neurogenic tumors as models for the study of growth, diagnosis, and therapy of spontaneous human brain tumors. We have also reported our study of intracranial gliomas and sarcomas induced in dogs by Rous sarcoma virus (RSV).

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Fig. 10. Periventricular glioma (X530).

Fig. 11. Subcutaneous scalp nodule (arrow) at site of virus inoculation.


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