Blood-brain barrier (BBB) function was studied in 14 normal dogs at time periods from 7 to 717 days after permanent insertion of 5- to 7-mCi seeds of iodine-125 ($^{125}\text{I}$) for interstitial radiation. The BBB function was measured with carbon-14-labeled alpha aminoisobutyric acid (AIB) and quantitative autoradiography, and expressed as a unidirectional blood-to-brain transfer constant, $K$. The $^{125}\text{I}$ radiation lesions consisted of three concentric histologically and functionally distinct zones: 1) a central zone of calcified necrosis; 2) a spongy fluid-filled zone; and 3) a narrow rim (2.6 ± 0.6 mm wide) of viable brain tissue with increased permeability. Within this rim, the mean value of the K of AIB was 5.8 times that of normal cortex. Over the 7- to 392-day time period the value of $K$ remained rather constant, and by 716 days $K$ values had returned to normal. There was moderate regional variation in the value of $K$; it was highest in the white matter and lowest in the gray matter surrounding the radiation lesion. The radiation lesion progressively increased in size from 7 to 80 days, after which there was little change. This study illustrates that the geographically circumscribed radiation from $^{125}\text{I}$ seeds is accompanied by similarly well-defined changes in BBB function, which may persist for over 1 year following insertion of the $^{125}\text{I}$ seed. This altered BBB function is probably responsible for the cerebral edema associated with $^{125}\text{I}$ interstitial radiotherapy.

KEY WORDS □ blood-brain barrier □ interstitial radiotherapy □ brachytherapy □ radiation necrosis □ beagle dog
the seed near the subcortical white matter beneath the coronal gyrus. Individual $^{125}$I seed activity varied between 5 and 7 mCi, as determined by the supplier. After $^{125}$I seed placement, the dogs were kept isolated but in a regular animal colony until experiments were performed 7 to 717 days later.

At the time of the experiments, the animals were fasted for 12 to 15 hours and anesthetized with xylazine and ketamine; these drugs were then administered as needed to maintain anesthesia. Catheters (PE-90 polyethylene tubing) were inserted unilaterally into the brachial artery and vein, and the animals were given 500 U heparin in 1 cc 0.9% NaCl. The arterial catheter was used to monitor blood pressure before and during the experiments and to obtain samples for blood gas determination and plasma for carbon-14 ($^{14}$C) analysis. The venous catheter was used to administer isotope.

**Experimental Procedures**

At the start of the experiment, 200 µCi of $^{14}$C-alpha aminoisobutyric acid (AIB, 40 to 60 mCi/mmol) was administered as an intravenous bolus. Timed arterial samples were obtained, cooled in ice, and centrifuged; 50 µl plasma was transferred to tared scintillation vials. Plasma samples were digested with 1.0 cc NCS tissue solubilizer, and plasma radioactivity was measured in a liquid scintillation counter with external standard Plasma samples were obtained, cooled in ice, and centrifuged; 50 µl plasma was transferred to tared scintillation vials. Plasma samples were digested with 1.0 cc NCS tissue solubilizer, and plasma radioactivity was measured in a liquid scintillation counter with external standard quench correction. At 45 minutes after AIB administration, each dog was killed with an overdose of sodium pentobarbital. The skull was lifted off with a Stryker saw, and the brain was removed within 2 to 3 minutes. The hemispheres were separated, cut in half, and frozen in liquid Freon cooled to $-40^\circ$C. After the location of the $^{125}$I pellet was verified by external survey with a Geiger-Mueller counter, each quarter of the brain was dipped in embedding matrix, tightly wrapped in a plastic bag, and stored at $-80^\circ$C prior to sectioning.

**Histological Study and Quantitative Autoradiography**

Tissue sections were prepared as previously described. Briefly, the brains were mounted on planchettes and serially sectioned 20 µm thick. Four sections of brain regions distant from the $^{125}$I seed were saved at intervals of 1 mm, and four sections of brain regions close to the $^{125}$I seed were saved at intervals of 50 µm. Sections were picked up on 2 x 3-in. glass slides and rapidly dried on a slide warmer at 65°C. Two of the four sections from each interval were fixed in formalin-ammonium bromide (2 gm NH$_4$Br/100 ml 10% formaldehyde solution) and stained with hematoxylin and eosin. The other two sections were placed in an x-ray cassette along with previously calibrated $^{14}$C methylmethacrylate standards and Kodak SB-5 x-ray film for an 8- to 12-week period of exposure.

Regional measurements of tissue radioactivity were obtained by means of computerized microradioscopy with a video-based digitizing system. Sequential measurements of optical density in each 75 x 75-µm element of $^{14}$C standards and tissue were made and stored in a computer. Optical density values were converted to tissue radioactivity by using the standard curve generated from each film with the $^{14}$C standards.

Regional measurements of the transfer constant, K, were obtained by using a computer-controlled cursor-outlining routine in conjunction with a processor. Selected tissue areas for study were defined from an adjacent histological section. The value of the unidirectional blood-to-tissue K of AIB for each tissue region was calculated from the following equation:

$$K = \frac{[C_i(T) - C_p(T)V_p]}{\int_0^T C_p(t)dt}, \quad (1)$$

where $C_i(T)$ is the tissue radioactivity value (nCi/gm) at the end of the experiment, T; $C_p$ is the plasma concentration of $^{14}$C-AIB (nCi/ml) during (t) and at the end (T) of the experiment; $C_p(T)V_p$ represents a vascular space correction for isotope remaining in the tissue at the conclusion of the experiment. The tissue plasma vascular space, $V_p$, was assumed to be 0.03 for these calculations. For each tissue region the K value represents the mean and standard deviation of all individual pixels within the area of interest, and the mean and standard deviation of the lower and upper 10% of all measurements within the area of interest. These latter values give a more realistic assessment of the range within an area than a single measurement alone.

Measurements were taken from regions around the $^{125}$I seeds, as delineated in Fig. 1. The necrotic center represented the central portion of the radiation-induced lesion, which was devoid of viable cells and was calcified. The spongy lucent zone represented a narrow rim between the calcified center and adjoining viable tissue. This zone was very irregular and often did not extend around the circumference of the necrotic zone. The cavity rim represented the zone of viable reactive tissue elements immediately surrounding the necrotic cavity. Measurements were taken from the entire circumference of the rim in which transcortical transport was increased, and in 500 x 500-µm blocks obtained radially from one cortical surface through the center of the lesion to the other cortical surface (Fig. 1). Additional measurements were taken from edematous gray and white matter and from normal-appearing gray and white matter in the ipsilateral and contralateral hemispheres.

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$^\dagger$ Aminoisobutyric acid was supplied by New England Nuclear, Boston, Massachusetts.

$\ddagger$ NCS tissue solubilizer manufactured by Amersham Corp., Arlington Heights, Illinois; and liquid scintillation counter, Model 300C, manufactured by Packard Instruments, Downers Grove, Illinois.

$\S$ Embedding matrix manufactured by Lipshaw Manufacturing Co., Detroit, Michigan.

$\|$ Carbon-14 standards manufactured by Amersham Corp., Arlington Heights, Illinois.
Effect of $^{125}$I on the blood-brain barrier

FIG. 1. Left: Schematic representation of the histology from Dog 9, Table 1. (A histological section from the same dog at the same level is shown in Fig. 2.) The central cavity represents the physical location of the $^{125}$I seed. N = the calcified central necrotic zone (cross-hatched area). L = the lucent zone, which was largely fluid-filled. The dashed line designates the outermost border of the cavity rim, C, inside which blood-brain barrier function is abnormal. Right: Plot showing mean values of the transfer constant, K, of alpha aminoisobutyric acid, transversely across the section in the plane shown (left) by the line and arrow. K was measured in 500 × 500-μ blocks. The plot illustrates the abrupt decrease in K values between the cavity rim and surrounding brain, with lower values in the lucent zone and necrotic center. CM = centimeters.

Evenly spaced histological sections and autoradiographic images were selected through each lesion and analyzed to obtain the distance from the pellet to the inner edge of the cavity rim (where viable tissue with BBB breakdown began) and to the outer edge of the cavity rim (where BBB function returned to normal). The cavity rim represents the zone of brain that received enough radiation to damage capillary endothelium, but not enough to cause tissue necrosis (Fig. 2). The serial sections were analyzed with the image-processing system described above, and volume measurements of the lesion were calculated, based on the trapezoidal rule, from which the mean inner and outer radii of the cavity rim were calculated.

FIG. 2. Reconstructed computer images of the transfer constant, K, of alpha aminoisobutyric acid (AIB) (left) and histological section (right) for Dog 9 in Table 1. The pseudocolor scale represents the K values of AIB, in units of ml/gm/min × 10⁴. The K values illustrate the sharply demarcated zone of blood-brain barrier (BBB) disruption around the $^{125}$I radiation lesion at 110 days after insertion of the $^{125}$I seed, as well as the regional variation in the magnitude of BBB disruption within this zone. An area of decreased K values is shown below and lateral to the pellet cavity, which corresponds to an area of edema in the histological section.
Results

The initial operative placement of the $^{125}$I seeds was tolerated well; the dogs were functionally normal in the initial postoperative period. Except for Dog 12, which survived for 392 days (Table 1), no abnormal neurological behavior or signs were observed. In Dog 12, focal seizures and a third nerve paresis were observed at Day 380 after $^{125}$I seed placement.

Physiological Status

At the time of the AIB experiments, all dogs had normal vital signs. Mean arterial blood pressure (± standard error of the mean) was 119.2 ± 7.2 mm Hg; $pO_2$ was 95.3 ± 4.1 torr; $pCO_2$ was 34.4 ± 2.2 torr; pH was 7.36 ± 0.05; and arterial hematocrit was 45.6% ± 1.0%.

Transfer Constant

Values of the transfer constant, $K$, were obtained from different regions around the pellet and from normal-appearing gray and white matter in the hemisphere ipsilateral to the $^{125}$I seed. These values are presented in Table 1. Measurements were also obtained from very small necrotic area (4.3 sq mm in cross section) and from gray and white matter in the contralateral hemisphere. These values are presented in the text. The lowest value of reliable measurements in these experiments, obtained from x-ray film background, was 0.0005 ml/gm/min.

Sequential Histological Changes

Sequential histological changes were analyzed from the serial frozen sections available from each animal. A very small necrotic area (4.3 sq mm in cross section) was present 7 days after $^{125}$I seed placement. This consisted of cellular debris with small numbers of polymorphonuclear and mononuclear cells; calcification was not present. By 30 days, calcification was observed around the $^{125}$I seed and the necrotic zone was 28.9 sq mm in maximum cross-sectional area. The calcified area was largely acellular but contained large thick-walled vascular structures which were filled with cellular debris and proteinaceous material. By 72 days, the calcified necrotic zone had reached a maximum cross-sectional area of 112 sq mm. In animals with longer survival times there was no further increase in the size of the calcified necrotic zone. At 716 and 717 days, the cross-sectional area of the necrotic lesion was 28.3 and 43.9 sq mm, respectively. This zone continued to contain structures which appeared to be large calcified vessels with thickened walls; a lumen could still be identified in most instances but was filled with proteinaceous material and there was no endothelial lining.

Immediately surrounding the necrotic cavity was a narrow area which we have termed the “lucent zone” (see Figs. 1 and 2) in reference to its appearance in the autoradiographic images. This zone was often irregular and discontinuous. It was present in a fragmentary fashion in dogs studied at 7, 21, and 30 days after $^{125}$I seed placement. From 43 to 175 days it was well defined; it varied from 0.1 to 1.0 mm in width, and separated the necrotic zone from the surrounding reactive viable brain tissue. Histologically, this lucent zone was spongiform, often filled with fluid, and contained macrophages and inflammatory cells. In the animals surviving 392, 716, and 717 days it was no longer present.

Immediately surrounding the cystic lucent zone was a region of reactive brain tissue. There were marked differences in the extent and nature of the appearance

### TABLE 1

*Value of the transfer constant, $K$, of alpha aminoisobutyric acid in different regions*

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Survival Time (days)</th>
<th>Necrotic Zone</th>
<th>Lucent Zone</th>
<th>Cavity Rim</th>
<th>Normal Cortex</th>
<th>Normal White Matter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Whole Rim</td>
<td>Highest 10%</td>
<td>Lowest 10%</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>3.9 ± 3.1</td>
<td>—</td>
<td>23.1 ± 11.6</td>
<td>46.1 ± 3.9</td>
<td>9.3 ± 0.7</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>7.0 ± 1.8</td>
<td>—</td>
<td>11.8 ± 5.2</td>
<td>24.2 ± 3.6</td>
<td>6.2 ± 0.7</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>7.1 ± 2.4</td>
<td>—</td>
<td>12.8 ± 3.2</td>
<td>17.5 ± 1.0</td>
<td>6.5 ± 2.1</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>17.8 ± 5.8</td>
<td>18.8 ± 6.1</td>
<td>23.2 ± 3.7</td>
<td>27.2 ± 0.1</td>
<td>15.7 ± 1.8</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>8.4 ± 2.3</td>
<td>5.6 ± 1.1</td>
<td>11.6 ± 4.3</td>
<td>21.3 ± 4.5</td>
<td>16.3 ± 2.0</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>7.4 ± 2.7</td>
<td>7.6 ± 2.2</td>
<td>11.5 ± 2.9</td>
<td>17.5 ± 1.8</td>
<td>7.2 ± 0.8</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>3.7 ± 3.2</td>
<td>5.9 ± 2.9</td>
<td>15.9 ± 8.8</td>
<td>37.9 ± 5.0</td>
<td>7.2 ± 1.8</td>
</tr>
<tr>
<td>8</td>
<td>87</td>
<td>6.7 ± 2.9</td>
<td>3.3 ± 1.6</td>
<td>10.0 ± 5.0</td>
<td>21.4 ± 4.2</td>
<td>4.0 ± 1.1</td>
</tr>
<tr>
<td>9</td>
<td>110</td>
<td>4.9 ± 2.9</td>
<td>4.5 ± 3.0</td>
<td>11.3 ± 5.5</td>
<td>23.3 ± 2.9</td>
<td>4.4 ± 1.0</td>
</tr>
<tr>
<td>10</td>
<td>149</td>
<td>3.1 ± 1.4</td>
<td>2.2 ± 2.0</td>
<td>8.9 ± 4.5</td>
<td>18.7 ± 4.5</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td>11</td>
<td>175</td>
<td>4.0 ± 3.0</td>
<td>3.5 ± 2.4</td>
<td>13.3 ± 7.6</td>
<td>27.7 ± 2.2</td>
<td>2.7 ± 1.1</td>
</tr>
<tr>
<td>12</td>
<td>392</td>
<td>5.3 ± 3.0</td>
<td>—</td>
<td>13.4 ± 2.0</td>
<td>30.2 ± 8.2</td>
<td>5.6 ± 1.7</td>
</tr>
<tr>
<td>13</td>
<td>716</td>
<td>2.9 ± 6.2</td>
<td>—</td>
<td>5.5 ± 5.4</td>
<td>15.2 ± 4.2</td>
<td>1.2 ± 1.4</td>
</tr>
<tr>
<td>14</td>
<td>717</td>
<td>8.0 ± 4.1</td>
<td>—</td>
<td>22.2 ± 17.01</td>
<td>56.9 ± 17.2</td>
<td>2.7 ± 1.6</td>
</tr>
<tr>
<td>averaged mean values</td>
<td>6.4 ± 3.8</td>
<td>6.4 ± 5.3</td>
<td>13.9 ± 5.4</td>
<td>27.5 ± 12.0</td>
<td>6.6 ± 4.6</td>
<td>2.4 ± 1.2</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviation × $10^3$, expressed as ml/gm/min, and were obtained in and around the $^{125}$I radiation lesion and in normal contralateral brain. For further explanation of the locations of different regions, see the text and Fig. 1. “Cavity rim” represents the viable rim of brain tissue in which the blood-brain barrier function is altered. Highest and lowest 10% represent the 10% of measured values at the high and low ends of the range, and give an indication of the range of K values within the cavity rim. — = not done: see text.

† These values were predominantly determined by a permeability increase in one gyrus overlying the $^{125}$I necrotic cavity (see text).
of white and gray matter in this region, which is referred to as the "cavity rim" since it surrounded the central necrotic cavity. In white matter extensive edema was present at 7 days after 125I seed placement and continued to 392 days (Fig. 2). Focal edematous changes could be identified in gray matter adjacent to the necrotic cavity, but this was never extensive. Blood vessels in both gray and white matter had swollen endothelial cells, were frequently surrounded by a few mononuclear or polymorphonuclear white cells, and sometimes appeared to be proliferating, especially in the dogs with longer survival. Reactive astrocytes were present in both gray and white matter, but were more numerous in the latter. Reactive changes in endothelial cells and astrocytes were limited to a zone 1 to 3 mm in width immediately surrounding the cavity.

Edematous changes were extensive in the hemisphere ipsilateral to the pellet in the animals that survived 7 to 392 days after 125I seed placement, and had resolved in the dogs that survived 716 to 717 days. White matter edema was severe in the centrum semiovale and in the ipsilateral normal-appearing white matter (Fig. 2). In dogs with survival times of less than 30 days, K value at 7 days to 7.7 times the normal cortex K value increased over normal brain values in all animals. The value of the transfer constant, K, of AIB was slightly greater than 0.03 ml/gm/min was observed where the cavity rim was located in the centrum semiovale. However, in other instances where the rim involved centrum semiovale, no such focal increases were seen. In the white matter, but not in the gray matter, increases in the K value were sometimes seen 4 to 5 mm distant from the junction between the lucent zone and cavity rim. No K

Sequential Changes in Transfer Constant

The value of the transfer constant, K, of AIB was 0.002 ml/gm/min in the normal cortex (contralateral to 125I seed placement) and 0.0007 ml/gm/min in the contralateral white matter. In the ipsilateral normal-appearing cortex, the K value was 0.002 ml/gm/min, and in the ipsilateral normal-appearing white matter it was 0.001 ml/gm/min. The values in corresponding regions of ipsilateral and contralateral brain were not significantly different (p > 0.05, Student's t-test).

In the necrotic zone, the K value of AIB was slightly increased over normal brain values in all animals. The value was initially low in the dog studied 7 days after 125I seed placement, peaked at 43 days, and then remained stable from 56 to 717 days (Table 1). The increases ranged from 1.7 times the normal cortex K value at 7 days to 7.7 times the normal cortex K value at 43 days, reaching a plateau at 1.3 to 3.2 times the normal cortex K value from 56 to 717 days. In each instance the increase over the normal cortex value was significant (p < 0.05, Student's t-test). Regionally within the necrotic zone, the K value was highest at the outer margin and lowest in the central part of the necrotic zone. Otherwise, regional variation of K within the necrotic zone was minimal (Fig. 2).

In the lucent zone, mean values of the transfer constant generally paralleled those of the necrotic zone, even though these two regions were distinct in both frozen histological sections and autoradiographs (Fig. 2). In dogs with survival times of less than 30 days, K values were not reported for the lucent zone since this zone was highly irregular and could not be distinguished adequately from the underlying necrotic zone or overlying cavity rim. In the 392- to 716-day studies the lucent zone was no longer present.

In the cavity rim, which represented the zone of viable reactive brain tissue surrounding the 125I pellet, the K value of AIB was increased above normal brain values in a circumferential rim of tissue that was generally 1 to 3 mm in width. The increase was present at 7 days after 125I seed placement (mean K 0.023 ± 0.011 ml/gm/min) and remained at 392 days (mean K 0.013 ± 0.002 ml/gm/min). At 717 days the mean K value was similar to that of normal contralateral cortex. In the 717-day study, there was marked asymmetry of BBB breakdown. Most of the increased K value occurred in a single overlying gyrus (see "Highest 10%" column, Table 1), while the bulk of the cavity rim had values approaching that of normal cortex (see "Lowest 10%" column, Table 1). Except in the animals studied at 716 and 717 days, the K values in the cavity rim were significantly higher than those of normal cortex or white matter (p < 0.0001, paired t-test). The averaged mean value of the K of AIB in the cavity rim was 0.014 ± 0.005 ml/gm/min (Table 1). Within each animal, there was moderate variation in K values, as indicated by the highest and lowest 10% of the values recorded (Table 1) and as illustrated in Fig. 2. Differences in the mean K values between animals are not directly comparable, since the anatomical location of the pellet was not identical in each instance. As a result of slightly different pellet locations, different brain structures and different amounts of gray and white matter were included in the measurements of each rim zone.

In individual animals, focal increases in K could often be correlated with histological features. In Dogs 1 and 2 (Table 1) the highest K values were associated with an area of cortex in which meninges extended into a sulcus in close proximity to the pellet (Fig. 2). The highest K value in this instance was 0.056 ± 0.001 ml/gm/min. In the animals sacrificed 717 days after 125I seed placement, the highest values were recorded in a gyrus that seemed to have been isolated by the radiation lesion. Despite the increased K values, this gyrus appeared histologically normal. Generally, when a K value greater than 0.03 ml/gm/min was observed in a gray matter structure, some corresponding morphological feature could be found, such as meninges, frank necrosis, or gray-white matter junction. No gray matter areas were observed with K values greater than 0.06 ml/gm/min.

In contrast, variation in K values in the white matter often could not be explained on a morphological basis. The highest K values in the white matter (0.057 ± 0.001 ml/gm/min) were observed where the cavity rim was located in the centrum semiovale. However, in other instances where the rim involved centrum semiovale, no such focal increases were seen. In the white matter, but not in the gray matter, increases in the K value were sometimes seen 4 to 5 mm distant from the junction between the lucent zone and cavity rim. No K
values greater than 0.06 ml/gm/min were observed in white matter. Away from the cavity rim, no increases in K values were seen in any other structures of the ipsilateral or contralateral hemisphere. Unexpectedly, decreases in K values were often seen in edematous white matter regions of the ipsilateral hemisphere. The mean K value of edematous white matter regions was 0.0006 ± 0.0006 ml/gm/min. Although in absolute terms this is not much lower than the normal white matter value of 0.0012 ± 0.0008 ml/gm/min, the difference is significant (p < 0.005, paired t-test). Areas of decreased K values associated with edematous brain regions are apparent in the digitized autoradiographs seen in Fig. 2.

Correlation Between Time, Dose, and Zone of BBB Breakdown

We measured the distance from the center of the necrotic cavity (the location of the 125I seed) to the inner and outer margins of the cavity rim (that zone in which BBB breakdown occurred). The results of these measurements are shown in Fig. 3, along with the theoretical maximum accumulated tissue radiation exposure at different distances from the 125I pellet. There was a rapid increase from 8.2 to 18.2 mm in the maximum cross-sectional diameter of the entire lesion from 7 to 72 days after 125I seed placement, with only a small increase after that (to a maximum diameter of 22.8 mm at 392 days). There was some variability of the maximum inner and outer radii, which will be discussed later. Despite the increase in the maximum diameter of the entire radiation lesion over time and despite the variability in the size of the lesions, there was only a very narrow rim of viable tissue in which BBB breakdown occurred. This varied in width from 1.8 mm in Dog 8 to 3.7 mm in Dog 12, with a mean (± standard deviation) of 2.6 ± 0.6 mm (Table 1).

Discussion

Even though the technique of placing radioactive sources into brain tumors, known as interstitial irradiation or brachytherapy, is not new, its application has been hampered by inability to predict the effect of treatment on the tumor and the impact of radiation on surrounding healthy brain. Clinically, tumor control has often been incomplete while brain edema has been a serious complication. Higher-energy gamma emitting sources, such as iridium-192 or gold-198, can affect brain at greater distances from the source than low-energy gamma sources, such as 125I, which permit the delivery of high local doses of radiation with a rapid fall-off in tissue dose rate over a short distance (Fig. 3). Interstitial irradiation with 125I causes sharply demarcated zones of necrosis in normal brain, but can induce extensive ipsilateral hemispheric edema, as well as demyelination and a proliferative astrocytic reaction.

We studied the effect of permanent interstitially
Effect of $^{125}$I on the blood-brain barrier

placed $^{125}$I seeds of 5- to 7-mCi activity in normal canine brain on the unidirectional blood-to-tissue transport of AIB. The study involved exposure periods of 7 to 717 days. We made six major observations, as follows. 1) Breakdown of the BBB occurs as soon as 7 days after $^{125}$I seed placement. 2) The entire radiation lesion enlarges rapidly from 7 to 72 days, increases more slowly from 72 to 392 days, and is relatively decreased in size at 2 years. 3) The radiation lesion can be divided into three histologically and functionally different zones: a) a central zone of calcified necrosis; b) a narrow fluid-filled zone largely devoid of cells surrounding the central zone; and c) a narrow rim of viable but damaged tissue in which there is breakdown of the BBB. 4) The zone of BBB breakdown was narrow (2.6 mm) and the magnitude of the increase in the transfer constant, K, of AIB over normal brain values (1.7 to 7.7 times) remained relatively level for up to 1 year after placement of the $^{125}$I pellet, before returning to more normal values at 2 years. However, even at 2 years there were focal areas of increased K values. 5) Increased K values of AIB, corresponding to increased permeability, were most marked in white matter as compared to gray matter, but in both there was regional variation in the K value of AIB throughout the radiation lesion. 6) In regions of white matter in the hemisphere ipsilateral to the pellet with histological evidence of edema, there was often a corresponding decrease in the transfer constant of AIB.

Perhaps the two most remarkable features of the permeability changes associated with $^{125}$I interstitial radiotherapy were the sharp demarcation of the BBB breakdown (illustrated in Figs. 1 and 2) and the rather constant magnitude of the BBB breakdown from 7 days to 1 year (see the "Cavity Rim" column, Table 1). We had expected the sharp demarcation of the radiation lesion, based on previous histological studies, and on the rapid fall-off in the cumulative radiation dose associated with $^{125}$I (Fig. 3). Variation in the size of the radiation lesion (Fig. 3) could be either due to the differences in the activity of the $^{125}$I seed (the supplier reported a variation in activity from 5 to 7 mCi) or due to different anatomical locations of the pellets, which were inserted freehand. Indeed, in the animals with the two largest lesions (Dogs 7 and 12, Table 1), the pellets were located deep in the white matter next to the lateral ventricle.

However, we had not anticipated that the magnitude of the BBB breakdown would remain at a nearly constant level from 7 to 392 days. We had expected progressive breakdown of the BBB over time, associated with progressively increasing values of the K of AIB. The fact that the K of AIB remained at rather constant levels implies that the brain capillaries have a limited ability to respond to damage caused by $^{125}$I gamma radiation. It will be very interesting to know whether this limited response is a general characteristic of brain capillaries to all forms of radiation or whether radiation of different energies or with different dose rates can produce differing degrees of BBB breakdown. Unfortunately, there are few quantitative data for comparison. There have been no quantitative studies of BBB function after high-dose temporary $^{125}$I interstitial radiotherapy.

A small number of quantitative measurements have been collected after externally administered gamma radiation. Caveness and coworkers studied blood-to-brain transfer of three compounds of different molecular weights in monkeys exposed to a single externally administered dose of 3500 cGy. Although their data were gathered over a single time period, the authors observed a relationship between the K of a compound and its molecular diameter, suggesting that the extent of BBB breakdown may differ for compounds with different lipid solubilities and molecular weights. In another study of BBB function with $^{14}$C-AIB, they noted increased permeability as late as 21 months after a single dose of 3500 cGy. Levin, et al., studies changed in capillary permeability of several compounds in rats after single-dose and multiple-fraction regimens with externally administered doses of 200 to 2500 cGy. They observed increased permeability of urea and dulcitol, but not the other compounds. It is not possible to compare these studies directly with ours, although the data suggest limited response characteristics of the BBB to gamma irradiation.

Studies of patients treated with externally administered gamma radiation have suggested a predictable relationship between the time-dose characteristics of the radiation and the development of radiation necrosis, even though there is a certain amount of variation from patient to patient. The radiation from interstitial $^{125}$I seeds differs from external-beam irradiation in that the dose rate is lower and tissue is exposed continuously to the radiation, rather than intermittently. It would be highly desirable to predict the size of the $^{125}$I radiation lesion and the zone of the BBB breakdown. Such an attempt is shown in Fig. 3. This diagram was made by plotting the inner and outer radius of the zone of BBB breakdown around each $^{125}$I seed in the present study. Inside the inner radius of BBB breakdown is the zone of radiation necrosis (which includes the lucent zone of our observations). Outside the outer radius, BBB function is normal. The estimate in Fig. 3 must be considered crude because the individual activity of the seeds varied in our study (between 5 and 7 mCi) and there was variation in the anatomical locations of the pellets. In Fig. 3 we have also shown the calculated cumulative radiation dose at different distances from a 6-mCi seed. This figure suggests that radiation necrosis develops in a region with a calculated exposure of 27,000 cGy or greater, and that BBB function is normal in tissue with an accumulated exposure of 13,500 cGy or less. These are very high values compared to the 5500 to 6000 cGy received by the brain from externally administered gamma radiation, above which dose the incidence of radiation necrosis increases rapidly. In the case of the $^{125}$I seeds, we
believe that the actual accumulated tissue radiation exposure is less than the calculated value, and that the difference is explained by the changing tissue absorbance characteristics, particularly after the central part of the radiation lesion begins to calcify. The calcified zone of radiation necrosis probably causes a gradual increase in the energy absorption coefficient of the tissue over time, which progressively limits tissue exposure outside the zone of calcified necrosis. If the estimates in Fig. 3 are correct, then calculations of $^{125}$I dosimetry may underestimate the size of the radiation lesion if conventional methods are used to calculate dosimetry. Conventional calculation methods assume a constant value for the tissue coefficient of absorption. Obviously, hemispheric edema cannot be explained by corresponding BBB breakdown in the areas affected by edema, nor can demyelination in areas remote from the seed be explained by direct radiation effect. Instead, the highly restricted disruption of normal BBB function (Figs. 1 and 2) serves as a source for diffusion and bulk flow of serum proteins into brain, a source that remains present for at least a year. Blasberg, et al., have shown that AIB is not a good marker of the processes associated with edema, since this small neutral amino acid is trapped intracellularly and cannot diffuse very far. The physiological mechanisms of $^{125}$I-induced hemispheric edema remain to be studied.

The ultimate goal of $^{125}$I interstitial radiotherapy is the treatment of brain tumors. It has been used in highly malignant and lower-grade malignant gliomas, and in an experimental study of avian sarcoma virus-induced canine brain tumors. The present study will hopefully allow the effects of $^{125}$I interstitial therapy on normal brain to be distinguished from effects on brain tumors, as quantitative studies proceed; it should also help to elucidate the mechanisms of the vasogenic edema associated with $^{125}$I interstitial radiotherapy.

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