Occurrence of Hemangiosarcomas in Beagles with Internally Deposited Radionuclides


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SUMMARY

In a series of related experiments to evaluate the relative toxicity of inhaled radionuclides, beagles were exposed to aerosols containing relatively soluble (chloride) or relatively insoluble (fused clay) forms of $^{144}$Ce and $^{89}$Sr. With the toxicity of inhaled radionuclides, beagles were exposed to aerosols containing relatively soluble (chloride) or relatively insoluble (fused clay) forms of $^{144}$Ce and $^{90}$Sr. The result was an aerosol of relatively soluble $^{144}$CeCl$_3$ or $^{90}$SrCl$_2$ and relatively insoluble $^{89}$Y, $^{89}$Y, $^{144}$Ce, and $^{90}$Sr in fused clay particles) forms of $\beta$-$\gamma$-emitting radionuclides. Dogs exposed to $^{144}$Ce and $^{90}$Sr in both the chloride and fused clay forms have developed various neoplasms at or near the sites of radionuclide localization. The finding of a high incidence of hemangiosarcomas in these animals during the 1st 7 years after exposure is addressed in this paper.

MATERIALS AND METHODS

The experimental design and methods for all 4 studies have been previously reported: $^{144}$CeCl$_3$ (1), $^{89}$SrCl$_2$ (24, 25), $^{144}$Ce-fused clay (14, 23), and $^{90}$Sr-fused clay (23, 25). These reports contain detailed data for experimental design, exposure methods, dosimetry, and early and late biological effects. Briefly, all dogs were raised in this colony and were 12 to 14 months old at exposure. Approximately equal numbers of males and females were exposed by inhalation to selected radioactive aerosols and are observed for their total life-span. Experiments have been underway with both relatively soluble ($^{137}$CsCl, $^{90}$YCl$_3$, $^{144}$CeCl$_3$, and $^{90}$SrCl$_2$) and relatively insoluble ($^{89}$Y, $^{89}$Y, $^{144}$Ce, and $^{90}$Sr in fused clay particles) forms of $\beta$-$\gamma$-emitting radionuclides. Dogs exposed to $^{144}$Ce and $^{90}$Sr in both the chloride and fused clay forms have developed various neoplasms at or near the sites of radionuclide localization. The finding of a high incidence of hemangiosarcomas in these animals during the 1st 7 years after exposure is addressed in this paper.
whole-body retention. The LTRB, or radioactivity remaining after this early clearance, was retained tenaciously. For the relatively insoluble fused clay forms, the initial lung burden was found to be equal to the LTRB. For the chloride forms, the relationship between initial lung burden and LTRB is less definite because material not initially associated with the lung, i.e., upper respiratory tract radioactivity, may also be absorbed into the systemic circulation from the gastrointestinal tract and contribute to the LTRB.

The dogs were housed individually in metabolism cages for 2 months after exposure and then transferred to kennels where they were housed 2 dogs/run. Dogs were continually observed, and given regular clinical, hemato logical, serum chemical, and radiological examinations. Dogs that died, or that were euthanized near death were given detailed gross and microscopic postmortem examinations. Selected tissues were also analyzed for $^{144}$Ce or $^{90}$Sr content.

RESULTS

The status of these 4 continuing studies up to January 1, 1974, is outlined in Tables 1 to 3. Table 1 lists the number of dogs in each experiment and the causes of death by general category. Early deaths were related to damage to organs receiving significant radiation doses due to distribution patterns of the radionuclide and its form. Table 2 lists types of neoplasms and related disorders that have occurred in all 4 experiments, and Table 3 includes the time to death, initial activities, and cumulative radiation doses to critical target organs.

After inhalation in the chloride form, $^{144}$Ce was translocated at a moderately rapid rate from lung to liver and skeleton leading to significant radiation doses to all 3 tissues (1). Dogs from this study died at relatively early times after exposure (less than 2 years) with bone marrow aplasia (9 dogs), radiation pneumonitis and pulmonary fibrosis (3 dogs), and hepatic necrosis (3 dogs).

Thirteen dogs exposed to $^{144}$CeCl$_3$ died or were euthanized after 2 years postexposure with neoplasms involving the 3 target organs. Five dogs (3 males and 2 females) developed primary hemangiosarcomas of the liver between 4.8 and 6.7 years after exposure. The immediate cause of death in 4 of 5 animals was i.p. hemorrhage from a ruptured hemangiosarcomatous cyst. All the dogs had some degree of anemia and icterus. The course of obvious clinical illness was generally quite short, 1 to 2 days in 3 dogs and 27 days in another, although 1 dog had a clinical illness of 185 days. One animal also had a small fibroma of the liver. The vascular tumors in 2 dogs were large solitary masses, whereas 3 dogs had multiple small and large tumors scattered through the liver. All the lesions were cystic and had extensive necrosis. Tumor masses measured from 1 to 3 mm to 15 cm in diameter and consisted of both small and large blood-filled cysts (Fig. 1). The tumors had a vari egated appearance, being mottled yellow to red to black and the cut surfaces being very hemorrhagic. In 3 dogs, there were metastases to lung. One of these also had metastases to kidney and 1 also had tumors in the omentum and mesentery. No splenic tumors were found. It is not known whether the multiple liver masses represented intrahepatic metastasis or multicentric origin.

Histologically, the tumors had both capillary and cavernous patterns of blood vessel formation. The neoplastic cells lining these vascular channels also varied in appearance. In some tumors the cells were quite plump with abundant cytoplasm and round to ovoid nuclei (Fig. 2). These cells generally had high nuclear to cytoplasmic ratios and often had multiple and bizarre nucleoli. In other tumors, the cells were spindle-shaped with relatively scanty cytoplasm and elongated ovoid nuclei (Fig. 3). However, nuclear to cytoplasmic ratios were still high and the nucleoli were abnormal. Mitoses were frequent and the tumors usually were locally invasive. Necrosis and fibrosis were prominent findings in all cases.

The bone-related hemangiosarcoma seen after $^{144}$CeCl$_3$ inhalation was a hemorrhagic, gelatinous mass of tissue that filled the right nasal cavity and invaded the olfactory lobe of the brain. Microscopically, most of the tissue was necrotic and only fragments of neoplasm were found. The tumor cells were similar to those described for the liver neoplasms. Three dogs developed squamous cell carcinomas of the maxillary region presumably arising from epithelium in close apposition to bone. Two of these dogs also had lung neoplasms; one had a pulmonary adenoma and the other had a bronchial adenosarcoma. Only 1 osteosarcoma was seen and this was at a relatively early time, 2.2 years after exposure. Only 1 control dog in the $^{144}$CeCl$_3$ study has died with a neoplasm and that was a thyroid carcinoma.

Inhaled $^{90}$SrCl$_2$ was rapidly translocated from lung to skeleton where it delivered most of its radiation dose and was avidly retained (25). Nine dogs, 6 $^{90}$Sr-exposed and 3 controls, were sacrificed at early times for radiobiological analysis and 6 dogs died early with bone marrow aplasia. All the neoplasms seen in the $^{90}$SrCl$_2$-exposed dogs involved liver or closely apposed tissues. Of the 29 dogs with neoplasms, 15 were females and 14 were males. Fifteen osteosarcomas and 12 hemangiosarcomas were observed. The range of cumulative radiation dose to skeleton in both groups was similar (850 to 18,000 rads). Nine females and 6 males had osteosarcomas and 8 females and 4 males had hemangiosarcomas. The fibrosarcomas occurred, 2 in males and 1 in a female. The 2 cases of leukemia, 1 a myelogenous and 1 a myelomonocytic form, were seen in a female and a male, respectively. A malignant giant cell tumor and a basosquamous carcinoma of the skull were both found in male dogs. The total numbers of dogs and tumors do not agree because 5 dogs, 4 females and 1 male, had both a hemangiosarcoma and an osteosarcoma. One control dog died with a fibrosarcoma of the chest wall.

Chart 1 is a histogram showing the distribution of bone-related neoplasms with time after exposure in the $^{90}$SrCl$_2$ study. Hemangiosarcomas appeared more frequently at early times and none have been seen since 6.5 years after exposure, whereas the incidence of osteosar-
Hemangiosarcomas in Radiated Dogs

Table 1
Causes of death in beagles after inhalation of 144Ce and 89Sr in soluble or relatively insoluble forms

<table>
<thead>
<tr>
<th>Radionuclide and form</th>
<th>No. of animals</th>
<th>No. of dead</th>
<th>Early deaths &lt; 2 yrs postexposure</th>
<th>Late deaths &gt; 2 yrs postexposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>144CeCl₂</td>
<td>55</td>
<td>28</td>
<td>15 bone marrow, pulmonary, or hepatic injury</td>
<td>13 neoplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 control</td>
<td>1 neoplasia</td>
</tr>
<tr>
<td>89SrCl₂</td>
<td>72</td>
<td>38</td>
<td>6 bone marrow injury</td>
<td>32 (39 neoplasia 3 miscellaneous)</td>
</tr>
<tr>
<td></td>
<td>25 controls*</td>
<td>3</td>
<td></td>
<td>3 (1 neoplasia 2 miscellaneous)</td>
</tr>
<tr>
<td>144Ce-fused clay</td>
<td>111</td>
<td>24</td>
<td>17 pulmonary injury</td>
<td>7 neoplasia</td>
</tr>
<tr>
<td></td>
<td>15 controls</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>89Sr-fused clay</td>
<td>72</td>
<td>45</td>
<td>32 pulmonary injury</td>
<td>13 neoplasia</td>
</tr>
<tr>
<td></td>
<td>12 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* As of January 1, 1974.
* Six animals exposed to 89SrCl₂ and 3 controls were sacrificed within 1 year postexposure and are not included in the tabulations of dead animals.

Table 2
Histological classification of neoplasms and related lesions in beagles after inhalation of 144Ce and 89Sr in soluble or relatively insoluble forms

<table>
<thead>
<tr>
<th>Organ</th>
<th>Radionuclide and form</th>
<th>Lung</th>
<th>Liver</th>
<th>Skeleton and closely apposed tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>144CeCl₂</td>
<td>1 pulmonary adenoma*</td>
<td>5 hemangiosarcomas</td>
<td>3 squamous cell carcinomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 bronchial adenocarcinoma*</td>
<td>1 fibroma</td>
<td>2 myelogenous leukemias</td>
</tr>
<tr>
<td></td>
<td>89SrCl₂</td>
<td></td>
<td></td>
<td>1 myeloproliferative disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 hemangiosarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 osteosarcoma</td>
</tr>
<tr>
<td></td>
<td>144Ce-fused clay</td>
<td>7 hemangiosarcomas</td>
<td></td>
<td>15 osteosarcomas* *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 fibrosarcoma*</td>
<td>1 bronchioloalveolar carcinoma*</td>
<td>12 hemangiosarcomas* *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 fibrosarcomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 myelogenous leukemias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 giant cell tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 basosquamous carcinoma</td>
</tr>
<tr>
<td></td>
<td>89Sr-fused clay</td>
<td>13 hemangiosarcomas</td>
<td></td>
<td>1 squamous cell carcinoma*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 bronchioloalveolar carcinoma*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* These tumors occurred in animals with another neoplasm (no dogs had more than 2 types of neoplasms considered to be radiation induced).
* Five dogs had both osteosarcoma and hemangiosarcoma.
* Four dogs had multiple primary osteosarcomas and 3 had multiple primary hemangiosarcomas. The totals do not reflect more than 1 primary neoplasm per dog.

Survival time was not significantly different in dogs with hemangiosarcomas and osteosarcomas.

The gross appearance of the hemangiosarcomas was generally similar among the dogs. The lesions varied in consistency but were usually composed of blood-filled cysts of various sizes in a trabecular pattern (Fig. 4). Tumors were often necrotic and sometimes, little solid tumor tissue could be found. The hemangiosarcomas ranged from 1 to 2

comas has remained fairly constant. Several additional osteosarcomas have been found since January 1, 1974, but no hemangiosarcomas. The primary skeletal distribution of the different types of bone sarcomas was not significantly different. The ribs (23%), pelvis (21%), scapula (13%), and skull (13%) were the most commonly affected sites. Relatively few bone sarcomas developed in the limb bones in contrast to similar lesions occurring spontaneously (19).
Table 3
Cumulative radiation doses to target organs in beagles that developed neoplasms after inhalation of 144Ce or 90Sr

<table>
<thead>
<tr>
<th>Radio-nuclide and form</th>
<th>Initial activity (µCi/kg body wt)</th>
<th>Death (yr post-exposure)</th>
<th>Oldest surviving dog (yr post-exposure)</th>
<th>Dose (rads)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>144CeCl₂</td>
<td>2.9-360 LTRB</td>
<td>2.2-7.6</td>
<td>8</td>
<td>3,900-6,200</td>
</tr>
<tr>
<td>90SrCl₂</td>
<td>1-120 LTRB</td>
<td>1.6-8.1</td>
<td>8.9</td>
<td>11,000-24,000</td>
</tr>
<tr>
<td>144Ce-fused clay</td>
<td>0.0024-210 ILB</td>
<td>2-3.6</td>
<td>6.1</td>
<td>29,000-61,000</td>
</tr>
<tr>
<td>90Sr-fused clay</td>
<td>3.7-94 ILB</td>
<td>1.8-3.3</td>
<td>3.9</td>
<td>43,000-67,000</td>
</tr>
</tbody>
</table>

* As of January 1, 1974.
* Doses expressed as average smear dose to target organs, i.e., total energy from decay/total mass of organ.
* ILB, initial lung burden.
* Calculated cumulative dose to nasal turbinates in the dog with nasal carcinoma was 3400 rads.

In summary, the most striking finding has been the high incidence of hemangiosarcomas in all 4 studies. A total of 5 hepatic hemangiosarcomas, 13 bone-related hemangiosarcomas, and 20 pulmonary hemangiosarcomas have been found to date. Perhaps even more surprising is the fact that every dog that has died with a neoplasm before 3.6 years after exposure to the relatively insoluble radionuclide forms developed a pulmonary hemangiosarcoma.

DISCUSSION

Although naturally occurring hemangiosarcomas are occasionally seen in some sites in dogs and have been reported after radiation in several species, the high incidence of tumors of endothelial origin in our studies is unusual. Several reviews of canine neoplasms (4, 30, 35, 38) indicate...
that hemangiomas and hemangiosarcomas are found primarily as tumors of skin and spleen. Hepatic hemangiomas and hemangiosarcomas of bone occur but the latter are uncommon. There have been a number of reports dealing specifically with endothelial neoplasms of the dog (2, 16, 27, 44). Meier (27) reported that 4% of more than 1500 canine tumors were vascular in origin and that about one-third were malignant. He listed the liver as a relatively common primary site after spleen and subcutis. Kleine et al. (16) emphasized that primary cardiac hemangiosarcomas are also common. In general, vascular tumors have been seen in older dogs.

Brodey (3), in a review of primary bone tumors in the dog, indicated that most were malignant and either osteosarcomas or chondrosarcomas. Of 230 bone tumors, only 6 (2.6%) were hemangiosarcomas and only 4% were found in small dog breeds (under 11 kg); the beagle was not represented. Ling et al. (19) reported on spontaneous primary canine bone tumors and found that most were malignant (sarcomas). Their series contained 8 primary bone hemangiosarcomas in 133 tumors (6%); 4 beagles were represented, 2 with osteosarcomas, 1 with a fibrosarcoma, and 1 with a hemangiosarcoma. Tumors of the canine respiratory system, including the nasal cavity, also have been reviewed. Tumors of the nasal cavity were frequent findings (28). Most were adenocarcinomas or squamous cell carcinomas, but mesenchymal neoplasms including fibrosarcomas, osteosarcomas and chondrosarcomas were also common. Beagles comprised 7% of the population showing these types of neoplasm. Reviews of primary lung neoplasms in dogs reveal only tumors of epithelial origin (5, 11, 31, 36). No well-documented cases of spontaneous primary malignant vascular neoplasms in the lung have been found in the literature. Primary hepatic tumors in the dog are not common neoplasms although tumors of endothelial, hepatic parenchymal cell, and bile duct origin are most frequently reported (30, 38).

A review of the literature on spontaneous canine neoplasms reveals that primary neoplasms of skeleton, lung, and liver are not among the more common tumors. This is especially true of primary hemangiosarcomas with perhaps the exception of the liver. Apparently, most of the tumors arising in our dogs that were exposed to 90Sr or 144Ce were irradiation induced. Since none of the neoplasms are unique to radiated dogs, however, the possibility that a small number of these tumors are spontaneous cannot be ruled out. This is especially true of the nasal cavity and hepatic lesions, although in both cases our tumors have appeared considerably earlier and more often than would be expected in an unexposed population. The absence of similar lesions in our control dogs also supports the radiation-related nature of these tumors.

A number of long-term dose response studies have been and are still being performed with internally deposited alpha- and beta-emitting radionuclides in beagles. The published results to date of these studies are outlined in Table 4. Fritz et al. (Ref. 13; T. E. Fritz, personal communication) reported only 2 hemangiosarcomas after injection of 144Ce citrate in beagles, 1 in liver and 1 in subcutis at the site of injection. Liver lesions consisted mainly of degenerative changes in the hepatic parenchyma. Several studies have been performed in beagles with 90Sr ingestion or injection (8, 9, 12, 33, 34, 41). In all cases, bone-related neoplasms, including squamous cell carcinomas of the nasal cavity or head sinuses and myeloproliferative disorders, were the major findings; however, hemangiosarcomas arising from the skeleton were also reported. Pool et al. (33, 34) reported that the incidence of hemangiosarcomas was less than 7% in dogs with bone sarcomas. Finkel et al. (12) found that 18% of their bone sarcoma-bearing dogs had hemangiosarcomas. Dougherty et al. (8) and Thurman et al. (41) had a 27% incidence of hemangiosarcomas in their bone sarcoma series. Deposition of various alpha-emitting radionuclides in the skeleton (22) and liver (40) has not led to development of vascular neoplasms in dogs. Park et al. (32) (W. J. Bair, personal communication) reported 2 hemangiosarcomas of lung and 4 tumors of vascular origin in thoracic lymph nodes in dogs that inhaled 239PuO2; however, all of the 24 dogs in this study had pulmonary carcinomas as well. The 41% incidence of hemangiosarcomas among the bone sarcomas seen at our institute after 144Ce or 90Sr exposure is higher than any of the other studies; however, as we have noted earlier, this incidence appears to be decreasing with time. Furthermore, considering that all of our dogs that developed neoplasms of the liver and lung had hemangiosarcomas, there appears to be a striking paucity of hemangiosarcomas in dogs exposed to 144Ce and 239Pu at other laboratories.

The occurrence of hemangiosarcomas after radiation in a variety of animal species, including man, is not in itself surprising. McClellan and Jones (26) in reviewing the literature on 90Sr-induced neoplasia noted 3 mouse studies in which vascular neoplasms were found, although the incidences were much less than 10% overall, and other studies with mice, rats, rabbits, monkeys, and pigs in which no vascular tumors were found. In a study of cats ingesting 90Sr, 1 hemangiosarcoma was seen out of 4 bone sarcomas (45). Only 1 study reports an incidence of hemangiosarcomas similar to that seen in our work. Loutit et al. (21) found that, in CBA mice given injections i.p. of 90Sr, the incidence of vascular neoplasms of bone was well above that of osteogenic tumors. Hepatic neoplasms have been seen in rats (29) and Chinese hamsters (6) after 144Ce administration, but tumors of vascular origin were only a small percentage of these (S. A. Benjamin, unpublished data). Among human malignant neoplasms developing after thorotrast administration, however, angiosarcomas (hemangioendotheliomas) have been reported to be the most frequent type (43). Relatively small numbers of pulmonary hemangiosarcomas have been reported in radiated animals. Aside from the tumors in beagles, low incidences of pulmonary hemangiosarcomas have been seen in rats exposed to 239PuO2 "fumes" (20), soluble 239Pu compounds (17), and intratracheally injected 144CeCl4 (7).

Several interesting speculations arise out of comparing the incidence of hemangiosarcomas found in our dogs with other dog studies. First, one can contrast the relative effects of alpha- and beta-radiation on the type of tumor found. It is
Table 4

<table>
<thead>
<tr>
<th>References</th>
<th>Radio-nuclide</th>
<th>Initial activity</th>
<th>Exposure method</th>
<th>Target organ</th>
<th>No. of animals with tumors or related disorders</th>
<th>Radiation-related tumor types</th>
<th>No. of tumor type</th>
<th>Death (yr post-exposure)</th>
<th>Cumulative dose to target organs (rads)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fritz (1974)[a]</td>
<td>**Ce</td>
<td>55.2–80.3 μCi/kg</td>
<td>i.v. injection</td>
<td>Skeleton</td>
<td>9</td>
<td>Osteosarcomas</td>
<td>4</td>
<td>&gt; 2.5</td>
<td>7,000 (av.)</td>
</tr>
<tr>
<td>Dungworth et al. (1970) (9)</td>
<td>**Sr</td>
<td>0.03–36 μCi/day</td>
<td>Ingestion</td>
<td>Skeleton</td>
<td>36</td>
<td>Myeloproliferative disorders</td>
<td>14</td>
<td>1.2–8.75</td>
<td>1000–15,500</td>
</tr>
<tr>
<td>Pool et al. (1972 (33); 1973 (34))</td>
<td>**Sr</td>
<td>7–500 μCi/kg</td>
<td>Injection, single and multiple, i.v., i.m., s.c., PL</td>
<td>Skeleton</td>
<td>37</td>
<td>Osteo(chondro)sarcomas</td>
<td>73</td>
<td>1.5–13</td>
<td>Not available</td>
</tr>
<tr>
<td>Dougherty et al. (1972 (8))</td>
<td>**Sr</td>
<td>0.6–98 μCi/kg</td>
<td>i.v. injection</td>
<td>Skeleton</td>
<td>12</td>
<td>Osteosarcomas</td>
<td>8</td>
<td>3.5 (av.)</td>
<td>~8700 (av.)</td>
</tr>
<tr>
<td>Mays and Dougherty (1972 (22))</td>
<td>**Ra</td>
<td>0.00577–11.9 μCi/kg</td>
<td>i.v. injection</td>
<td>Skeleton</td>
<td>187</td>
<td>Osteo(chondro)sarcomas</td>
<td>160</td>
<td>&gt; 1.5</td>
<td>(60–18,000)</td>
</tr>
<tr>
<td>Taylor et al. (1972 (40))</td>
<td>**Pu</td>
<td>0.00055–3.3 μCi/kg</td>
<td>i.v. injection</td>
<td>Liver</td>
<td>10</td>
<td>Bile duct adenomas</td>
<td>8</td>
<td>7.6–13.2</td>
<td>Not available</td>
</tr>
<tr>
<td>Park et al. (1972 (32))</td>
<td>**Pu</td>
<td>0.2–3.3 μCi/kg</td>
<td>Inhalation</td>
<td>Lung</td>
<td>24</td>
<td>Bile duct carcinomas</td>
<td>2</td>
<td></td>
<td>200–12,000</td>
</tr>
</tbody>
</table>

Some dogs had more than 1 primary neoplasm and more than 1 type.
[b] Dose to femur.
[c] PL, via placenta.
[e] W. J. Bair, Battelle Northwest Laboratories, Richland, Wash., personal communication.

readily evident that β-radiation of canine lung, liver, and skeleton from **Sr or 144Ce is more likely to produce vascular neoplasms than α-radiation. Vaughan (42) in reviewing skeletal tumors induced by internal radiation supports this thesis and suggests that the range of the radiation in the tissues, specifically bone and marrow, is the determining factor. She suggests that more penetrating radiations induce malignant transformation in stem cells both of the endosteum and marrow elements and that angiomatous tumors arise in the marrow rather than from osteogenic tissue. Thus, the α particles, which have a short range in tissue, affect mainly the osteogenic components. With respect to the soft tissue tumors, and especially the lung, the relative paucity of vascular tumors after α-radia-
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Fig. 1. Liver from dog exposed to $^{144}$CeCl$_3$. There is a hepatic hemangiosarcoma showing hemorrhagic cysts and light-colored areas of necrosis.

Fig. 2. Photomicrograph of hepatic hemangiosarcoma showing plump angioblasts lining small and large blood vascular channels. H & E, × 400.

Fig. 3. Photomicrograph of a primary hepatic hemangiosarcoma from a dog which inhaled $^{144}$CeCl$_3$, showing extensive invasion of spindle cells between liver cords. H & E, × 185.

Fig. 4. Hemangiosarcoma involving the rib cage of a dog exposed to $^{89}$SrCl$_2$, showing both small and large blood-filled sinuses. a, pleural surface; b, external cut surface.

Fig. 5. Primary bone-related hemangiosarcoma from dog exposed to $^{89}$SrCl$_2$. The tumor tissue forms solid cords and cavernous vascular spaces. H & E, × 140.

Fig. 6. Photomicrograph of a primary bone-related hemangiosarcoma in a dog that inhaled $^{89}$SrCl$_2$, showing tumor cells forming capillary channels. H & E, × 450.

Fig. 7. Primary pulmonary hemangiosarcoma in dog that inhaled $^{89}$Sr-fused clay particles. There are multiple hemorrhagic tumor masses in the lung.

Fig. 8. Photomicrograph of a primary pulmonary hemangiosarcoma from a dog that inhaled $^{89}$Sr in fused clay particles showing solid tumor cords and large and small blood vascular spaces. H & E, × 100.

Fig. 9. High-power photomicrograph of a pulmonary hemangiosarcoma in a dog that inhaled $^{89}$Sr in fused clay particles. This neoplasm formed a loose capillary work. H & E, × 380.
Occurrence of Hemangiosarcomas in Beagles with Internally Deposited Radionuclides


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