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COMPARATIVE TOXICITY OF STRONTIUM-90 AND RADIUM-226 IN BEAGLE DOGS

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Report of Second Year, 12/16/90-12/15/91 and
Continuation Proposal for Third Year, 12/16/91-12/15/92

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EXECUTIVE SUMMARY

We are completing a 30-year study of the biological effects of ^{90}Sr and ^{226}Ra in the beagle in order to predict the possible long-term hazards to people from chronic exposure to low levels of irradiation. Animals received either radionuclide by several means of administration: (a) continual ingestion of ^{90}Sr, (b) a single intravenous injection of ^{90}Sr, or (c) a series of eight intravenous injections of ^{226}Ra. Although administration of ^{90}Sr and ^{226}Ra ended at 540 days of age, the animals continued to receive chronic, low-level radiation doses from these bone-seeking radionuclides throughout life. This project is the largest single cohort study in beagles of internally deposited radionuclides. It is unique in use of the ingestion route for ^{90}Sr and in exposures that began before birth and continued throughout development to adulthood with uniform labeling of the skeletons with ^{90}Sr. The last of the dogs died in 1986 at age 18.5 years, but we are continuing to investigate the significance of these long-term exposures given at low dose rates with regard to cancer production, physiologic well-being, and shortening of life through the detailed records that were kept and by study of preserved materials. All the data have been successfully accumulated and entered into a main-frame computer data base management system. Current work is exclusively directed at preparing research papers summarizing the results and the associated biostatistical and survival analyses.

INTRODUCTION

The major goal of this study on the toxicity of ^{90}Sr and ^{226}Ra is to provide information on long-term consequences that might occur in people from chronic exposure to α- and β-emitting bone-seeking radionuclides. To meet this goal, we are evaluating the biological effects of the two radionuclides in the beagle. Similarities between dogs and people provide a valuable basis for the scaling of potential hazards from radionuclide contamination from canine to human populations.

BACKGROUND

Radium-226 was injected intravenously into dogs beginning at 435 days and every two weeks thereafter until 540 days of age to relate to human radium dial-painter exposures. Activities over an approximately 500-fold range were administered to these animals in 6 treatment levels plus controls; together they comprise the R-dogs (Table 1). Strontium-90 was administered in the food, with the dietary concentration of ^{90}Sr maintained at a constant level with respect to dietary calcium levels to temporally simulate environmental exposure via the food chain. Activities were administered in 7 treatment groups (plus controls) over a 1500-fold range; these are the D-dogs (Table 2). Two additional small groups of dogs (S-dogs) were given their ^{90}Sr as a single injection at 540 days of age, to serve in the comparison of the two modes of administration (injection vs. ingestion).

Table 1. Experimental Design and Status of Radium-226 Toxicity Study.

^{226}Ra Injection Series (8 Biweekly Injections Starting at 435 Days of Age)					
Treatment Code	Multiple of 10 level	kBq/kg/inj	Total (kBq/kg)	Number of Dogs	Median Survival (Years)
R00	0	0	0	82	14.6
R05	0.33	0.099	0.789	46	14.5
R10	1	0.296	2.37	39	13.8
R20	6	1.74	13.9	42	10.9
R30	18	5.18	41.4	41	7.4
R40	54	15.5	124.0	41	5.1
R50	162	46.3	370.0	44	4.3
				335	

Table 2. Experimental Design and Status of Strontium-90 Toxicity Study.

^{90}Sr Ingestion Series (in utero to 540 days of Age) (Data includes 15 dogs fed throughout life in D30, D40 and D50)						
Treatment Code	Multiple of 10 Level	kBq ^{90}Sr per g dietary Ca	Ingested kBq/d	Total Ingested (kBq)	Number of Dogs	Median Survival (Years)
D00	0	0	0	0	80	14.5
D05	0.3	0.259	0.74	370	78	14.2
D10	1	0.777	2.59	1,480	40	13.5
D20	6	4.55	16.3	8,880	65	14.4
D30	18	13.7	48.1	25,900	72	14.1
D40	54	41.1	148.0	81,400	65	12.0
D50	162	123.0	444.0	241,000	64	5.2
D60*	486	370.0	1,332.0	718,000	19	2.2
					483	

*D60 dogs were not in the original experimental design but were added in 1967.

^{90}Sr Injection Series (Single IV Injection at 540 Days of Age)					
Treatment Code	Multiple of 10 Level	kBq/kg/inj	Total kBq/kg	Number of Dogs	Median Survival (Years)
S20	6	137	137	20	13.5
S40	54	1,220	1,220	25	13.3
				45	
Total				863	

PROGRESS REPORT

Survival

The cumulative survival rates of R05- and R10-level dogs appear indistinguishable from control animals through 17 years. Cumulative survival rates of other treatment groups are significantly different from controls ($p < 0.05$) after 7.5 years of age for R20 dogs, 6 years for R30s, 5 years for R40s, and 3 years for R50s.

Strontium-90 fed dogs at D05, D20, and D30 levels were not different from controls through 17 years of age, whereas D40s were significantly different from controls from 3 to 6 years and after 10 years of age; D50s after 3 years of age; and D60s after 2 years of age. The median survival time for unirradiated control beagles is 14.5 yr for D00's and 14.6 yr for R00's. Median survivals for each of the dose groups are given in Tables 1-2, above.

Radiation Doses

During the first year of this project, the dosimetry for each dog was completely reevaluated and revised to adjust for background in the ^{90}Sr studies, add ^{210}Po to the ^{226}Ra dosimetry, and adjust to a beagle skeleton assumed to be 10% of the body weight of a young adult. Since the marrow is not irradiated by alpha as radiation associated with ^{226}Ra and progeny, the marrow-free skeleton of 8% of young adult body weight was used for recalculation of ^{226}Ra doses. Cumulative average skeletal doses and standard deviation for each dose level are given in Tables 3 - 5.

Analysis of Radiation Effects

The main radiation induced effects from ^{226}Ra alpha irradiation were bone tumors, radiation osteodystrophy, and tumors of the eye. The spectrum of effects from beta irradiation in the ^{90}Sr-fed beagles included myeloid leukemia, bone sarcoma, squamous cell carcinoma of periodontal origin, nasal carcinomas, and various cancers of the oral cavity. The tumor dose-response relationships demonstrated thresholdlike properties with few if any effects in the lowest dosage levels. There were no bone sarcomas in the lowest 2 exposure groups for ^{90}Sr- fed beagles or in the lowest exposure group of the ^{226}Ra-injected beagles, but there were a total of 5 (2 fatal) in the controls. The RBE for the induction of bone tumors for ^{226}Ra alpha irradiation with respect to ^{90}Sr beta irradiation was a function of dose-rate varying from about 1 at about 0.2 Gy/d to about 30 at the lower dose rates. Primary ocular neoplasia was noted in 16 of the 863 beagles (14/16 were melanoma), although this cancer was usually not fatal due to early treatment. Thirteen of the 16 animals with the disease had been exposed to ^{226}Ra. Two dogs had been fed ^{90}Sr and one had been singly injected i.v. with ^{90}Sr.

Bone Tumors

The observed number of fatal skeletal sarcomas and total sarcomas (includes incidental and multiple tumors) for all of the dogs in these studies are summarized in Tables 3-5. There were no bone sarcomas in the lowest exposure groups D05, D10, and R05, but there were a total of 5 (2 fatal) in the controls.

A detailed study has been performed of the skeletal distribution of those sarcomas observed in ^{90}Sr-fed beagles and in 162 unexposed controls combined from all groups. The skeletal locations of these tumors are shown in Fig. 1. Regression analysis was used to relate the distribution of the tumors in 17 bone groups of ^{90}Sr-fed beagles to the various characteristics of these groups including bone surface distribution, mass of skeletal group, fraction of whole skeleton, mass of marrow-free skeleton, and relative proportion of cancellous and compact bone. Also, the relative dose to each of these groups over the life time of the beagles was compared tumor distribution. No significant correlations or meaningful trends were detected. The distribution of the tumors appears to be random, except that there were no tumors in paws, tail, or sternum. The observed total of 66 bone sarcomas in 47 beagles includes 49 osteogenic and 17 non-

osteogenic lesions. Among the latter 17 were four types, namely: chondrosarcoma (2 cases), hemangiosarcoma (4 cases), fibrosarcoma (9 cases), and undifferentiated sarcoma (2 cases). These 17 non- osteogenic sarcomas developed in 16 dogs. Their distribution, expressed as number of cases over number dogs with bone tumors, was 3/4 among pooled controls, 3/4 in D30, 6/10 in D40, 3/19 in D50, and 2/10 in D60.

Table 3. Selected results of lifetime ^{90}Sr toxicity studies in beagles receiving ^{90}Sr in food from midgestation until 540 days of age (D-series) at the University of California, Davis.

Dosage Level	Number of Dogs M	F	Total Ingested (kBq)	Median Survival Age (y)	Skeletal Dose (Gy ± SD)	Fatal Sarcomas M	F	Total Sarcomas M	F	Age at Onset (y)
D00	40	40	0	14.5	0	2	0	2	2	15.3
D05	38	40	370	14.2	0.4 ± 0.2	0	0	0	0	--
D10	21	19	1,480	13.5	1.2 ± 0.3	0	0	0	0	--
D20	33	32	8,880	14.4	6.7 ± 2.0	0	0	0	0	--
D30	38	34	25,900	14.1	22.5 ± 5.7	4	0	4	0	13.4
D40	30	35	81,400	12.0	50.4 ± 18.0	5	5	5	5	11.1
D50	32	32	241,000	5.2	80.2 ± 35.2	5	12	9	20	7.8
D60	12	7	718,000	2.2	107. ± 32.	7	3	13	5	2.3
TOTAL	244		239			24	20	33	32	

Table 4. Selected results of lifetime ^{90}Sr toxicity studies in beagles receiving a single intravenous injection at 540 days of age (S-series) at the University of California, Davis.

Dosage Level	Number of Dogs M	F	Total Injected (kBq/kg)	Median Survival Age (y)	Skeletal Dose (Gy ± SD)	Fatal Sarcomas M	F	Total Sarcomas M	F
S20	10	10	137	13.5	6.7 ± 2.3	1	0	1	0
S40	10	15	1,220	13.3	54.3 ± 18.1	3	3	3	3
TOTAL	20	25				4	3	4	3

Table 5. Selected results of lifetime ^{226}Ra toxicity studies in beagles receiving eight fortnightly intravenous injections from 435 to 540 days of age (R-series) at the University of California, Davis.

Dosage Level	Number of Dogs M	F	Total Injected (kBq/kg)	Median Survival Age (y)	Skeletal Dose (Gy ± SD)	Fatal Sarcomas M	F	Total Sarcomas M	F
R00	41	41	0	14.6	0	0	0	1	0
R05	21	25	0.789	14.5	0.9 ± 0.2	0	0	0	0
R10	20	19	2.37	13.8	3.0 ± 1.1	3	1	4	1
R20	20	22	13.9	10.9	13.9 ± 3.5	12	14	15	21
R30	21	20	41.4	7.4	31.6 ± 6.5	19	15	25	21
R40	19	22	124.0	5.1	77.6 ± 22.9	19	21	25	30
R50	24	20	370.0	4.3	167. ± 44.	13	12	20	18
TOTAL	166	169				66	63	89	91

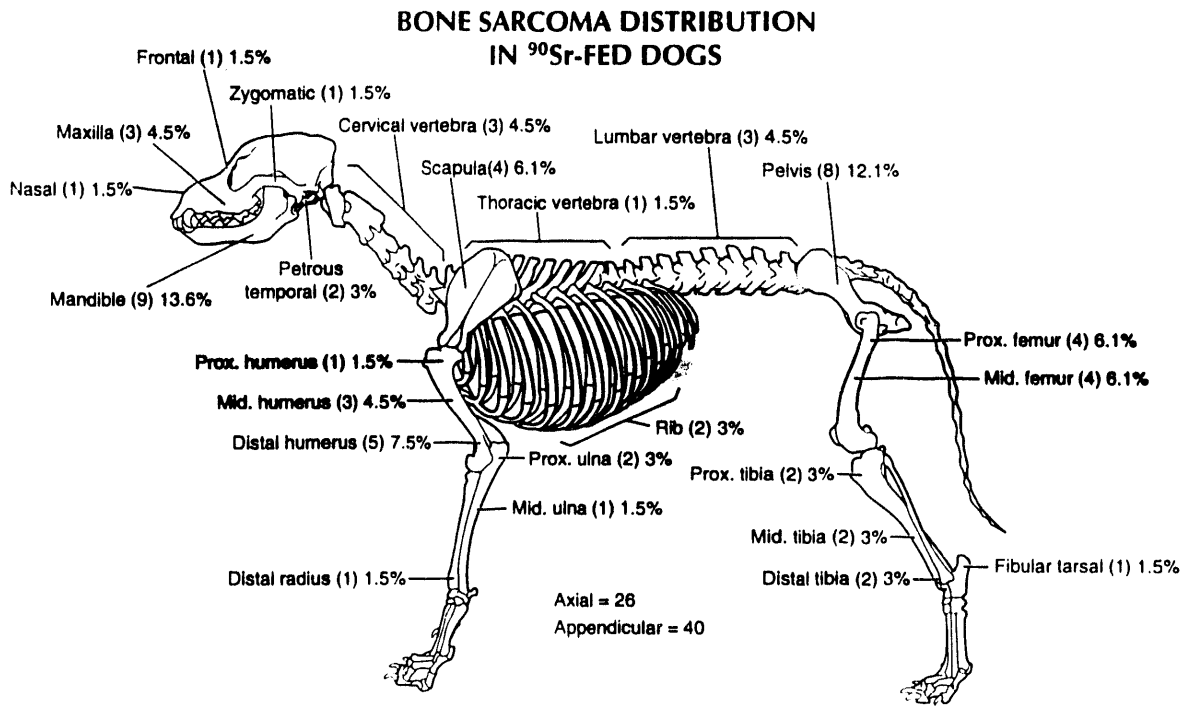

Figure 1. Total observed skeletal sarcomas by location with numbers observed and relative percent for ^{90}Sr-fed beagles.

Ocular Tumors

Primary ocular neoplasia was noted in 16 of the 863 beagles in this study. Thirteen of the 16 animals with the disease had been exposed to ^{226}Ra. Two dogs had been fed ^{90}Sr and one dog had been injected i.v. with a single dose of ^{90}Sr. The predominant tumor type (14/16 or 87.5%) was melanoma. The remaining tumors were either meningioma, derived from the optic nerve, or a ciliary body tumor, derived from like tissue. Four of the 16 tumors, all melanomas, were malignant. Three of those four resulted in widespread metastasis, emanating from this primary ocular site, and in each case melanoma was the cause of death. Primary ocular tumors in the three ^{90}Sr dogs were all found to be benign melanomas. Peto analysis showed that these tumors were significantly related to the exposure to ionizing radiation, since these tumor types are extremely rare (none observed in control dogs).

PLANS FOR NEXT YEAR

Work continues to finalize and document the results of this lifetime beagle study of ^{90}Sr and ^{226}Ra in bone. This effort will be limited to writing research papers, performing the supportive biostatistical analyses for these papers, and the publication of these papers. Emphasis continues to be on the carcinogenic responses in the beagle of skeletal burdens of ^{90}Sr and ^{226}Ra, and the highest priority is publication of definitive pathological, clinical, radiobiological, biomathematical and risk analysis reports of our finding in the most prestigious scientific journals.

This project involves several scientist who work a small fraction of their time on the project and usually donate time in excess of the available compensation. Those involved in this work include principal veterinary pathologists (Culbertson, Cain, and Spangler), clinical veterinarian (White), radiobiologist (Raabe), biophysicist (Parks), computer programmer/analyst (Burton), a skilled biostatistician-epidemiologist (Samuels) and a part-time scientific editor.

The papers currently in preparation, the lead author of each, and current status are listed below.

1. "Lifetime uptake and retention of ^{90}Sr and ^{226}Ra in beagles," O.G. Raabe and N.J. Parks, Radiation Research, Submitted, favorably reviewed, and in process.

2. "Occurrence of nasal carcinomas in beagles fed ^{90}Sr," G. Cain, et al., draft written, for submission to Radiation Research about December, 1991.

3. "Cancer risks from ^{90}Sr for intake from before birth until adulthood," O. Raabe, M.R Culbertson, R. White, et al., for submission January, 1991.

4. "Bone cancer and radiation injury risks induced by ^{226}Ra in beagles," O.G.Raabe, and S. Samuels, submitted to Health Physics, 1991.

5. "Comparative bone cancer risk induced by ^{90}Sr and ^{226}Ra in beagles," O.G. Raabe, et al., for submission November, 1991.

6. "Ocular tumors induced by ^{226}Ra and ^{90}Sr in beagles," R. White, et al., for submission December, 1991.

7. "Myeloproliferative disease in beagles with skeletal burdens of ^{90}Sr," G. Cain, et al., for submission, November, 1991.

8. "Skeletal distribution of ^{90}Sr-induced tumors in beagles," R. White, M.R. Culbertson, et al., for submission October, 1991.

9. "Skeletal distribution of ^{226}Ra-induced tumors in beagles," R. White, M.R. Culbertson, et al., for submission November, 1991.

10. "Concerning the relative biological effectiveness for carcinogenesis of high and low linear energy transfer bone seeking radionuclides," O.G. Raabe, et al., for submission September, 1992.

PAST PUBLICATIONS

1. "Interspecies scaling of risk from radiation-induced bone cancer," O.G. Raabe, L.S. Rosenblatt, and R.A. Schlenker, Int. J. Radiat. Biol. 57: 1047-1061, 1990.

NEW PUBLICATIONS (Reprints Enclosed)

1. "Comparative radiation-induced effects in bone and ocular tissue by ^{226}Ra and ^{90}Sr exposures to beagles in lifetime studies," R.G. White, M.R. Culbertson, L.S. Rosenblatt, N.J. Parks, S.J. Samuels, and O.G. Raabe, Joint Bone Radiobiology Workshop, Toronto, Canada, July 12-13, 1991, UCD-472-136, pp. 17-22, 1991.

2. "Skeletal uptake and lifetime retention of ^{90}Sr and ^{226}Ra in beagles," O.G. Raabe and N.J. Parks, Joint Bone Radiobiology Workshop, Toronto, Canada, July 12-13, 1991, UCD-472-136, pp. 23-28, 1991.

3. "Radionuclide distribution dynamics in skeletons of beagles fed ^{90}Sr: Correlation with injected ^{226}Ra and ^{239}Pu," Norris J. Parks, Health Physics 60: 343-351, 1991.

END

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