Radiation Carcinogenesis in Dogs Irradiated During Prenatal and Postnatal Development

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(Received December 6, 1990)

Dog/Co-60/Prenatal and Postnatal Development/Carcinogenesis

To evaluate the lifetime hazards of ionizing radiation exposure, 1680 beagles received whole-body, 60-Cobalt gamma exposures or sham-exposures during development. Eight groups of 120 dogs each received mean doses of 16 or 83 cGy at 8 (preimplantation), 28 (embryonic), or 55 (late fetal) days postcoitus (dpc), or 2 (neonatal) days postpartum (dpp). One group of 120 dogs received 83 cGy at 70 dpp (juvenile), and one group of 240 dogs received 83 cGy at 365 dpp (young adult). Sham-irradiations were delivered to 360 controls. Sexes were equally represented. Young dogs, up to 4 years of age, had an increase in benign and malignant neoplasms after irradiation in the perinatal period at 55 dpc or 2 dpp. Among these, 4 fatal cancers were observed. No malignancies occurred in comparably-aged controls. The increase in both fatal neoplasms and all neoplasms in the perinatally-exposed groups were statistically significant. Over the full lifetime, dogs irradiated in the perinatal period also had the strongest evidence for an increased risk for fatal malignancies of all types. Though not as strong, there was a trend for increased risk for fatal cancer in dogs irradiated at all other ages. The risk of fatal malignancy after irradiation was greater in females than in males. Dogs exposed at 55 dpc had a significant increase in lymphoid neoplasia and dogs exposed at 8 and 55 dpc had increased risk for hemangiosarcoma. There was no evidence for an increased risk for mammary carcinoma in irradiated females. Dogs exposed as juveniles at 70 dpp had a significant increase in all benign and malignant thyroid neoplasms, including fatal thyroid carcinoma.

INTRODUCTION

Among the most controversial topics relating to radiation carcinogenesis is the question of prenatal sensitivity. Initial reports from the Oxford Survey (Stewart et al. (1956, 1958)1,2) of an association between low-level diagnostic X-ray exposures in utero and increased risk for childhood cancer were confirmed by some subsequent epidemiologic studies (Ford et al. (1959)3, Diamond et al. (1973)4, Shiono et al. (1980)5, Harvey et al. (1985)6, Hopton et al. This study was supported in part by U.S. Public Health Service contract FDA 223–83–6028 from the Center for Devices and Radiological Health, Food and Drug Administration and Colorado State University.
but not by others (Jablon et al. (1970)\textsuperscript{8}, Oppenheim et al. (1974)\textsuperscript{9}). Periodic reevaluations of various sets of data from the Oxford Survey (Mole (1974)\textsuperscript{10}, Totter et al. (1981)\textsuperscript{11}, Kneale et al. (1986)\textsuperscript{12}, Bithell et al. (1988)\textsuperscript{13}) and other studies (MacMahon et al. (1962)\textsuperscript{14}, Monson et al. (1984)\textsuperscript{15}) have been conflicting and have not resolved the issue. Until recently, there was no information on the lifetime risk for prenatally irradiated persons. Yoshimoto et al. (1988)\textsuperscript{16} reported an increased risk of cancer over a 40 year period among the in utero exposed atomic bomb survivors. This further suggested that susceptibility to radiation-induced cancers was higher in persons irradiated prenatally compared with those irradiated as adults.

It has been stated frequently that there are few data from animal studies to suggest that the fetus has an unusually high sensitivity to radiation carcinogenesis (Monson et al. (1984)\textsuperscript{15}, Harvey et al. (1985)\textsuperscript{6}, Miller et al. (1986)\textsuperscript{17}). However, rather than animal evidence being absent with respect to this question, it is conflicting, probably due to the varied species and strains of animal used, and differing experimental conditions employed (Sikov (1981, 1989)\textsuperscript{18,19}).

The Collaborative Radiological Health Laboratory at Colorado State University has conducted a study to determine the lifetime hazards associated with prenatal and early postnatal exposure to ionizing radiation. The primary experiment was a life-span study in beagles given a single exposure to 60-Co gamma radiation to determine the role of age at exposure as a factor influencing radiation injury. A major endpoint in this study has been the induction of neoplasms. This paper reports the major findings with respect to carcinogenicity from the life-span study.

**MATERIALS AND METHODS**

A total of 1680 beagles (equal numbers of males and females) received either a single, whole-body exposure to 60-Co gamma radiation or a sham-exposure. Exposures were bilateral for a total of 10 minutes. Exposures were during prenatal development at 8, 28, or 55 days of gestation (days postcoitus or dpc), or during postnatal life at 2, 70, or 365 days of age (days postpartum or dpp). The gestation period of the dogs is approximately 63–64 days. The experimental design for the study is shown in Table 1.

The procedure for the radiation exposures and dosimetry have been reported (Angleton et al. (1977)\textsuperscript{20}, Angleton (1978)\textsuperscript{21}). Each dog was assigned an individual absorbed dose and the means and ranges for these are given in Table 2. The overall mean doses for dogs exposed at 20 and 100 R were 16 and 83 cGy (rad), respectively. A subset of the dogs (337) were sacrificed at 5, 8, or 11 years of age. Not enough dogs remained for a 14 year sacrifice group. A total of 1,343 dogs were allowed to live out their full life-span. The number of animals per group are shown in Table 3. Details of the experimental protocols and animal care have been reported (Angleton et al. (1988)\textsuperscript{22}). Dogs were entered into the study groups as whole litters, which was necessitated by the prenatal exposures.

Dogs were housed outdoors in federally inspected and approved facilities, were fed
Table 1. Experimental design of Life-Span Study.

| Age at Exposure | Exposure (R) | 0 | 20 | 100 |
|-----------------|--------------|---|----|-----|
|                 | Sex | L<sup>a</sup> | S<sup>b</sup> | L | S | L | S |
| Prenatal:       |     |               |               |   |   |   |   |
| 8 dpc<sup>c</sup> | M   | 20           | 10           | 40 | 20 | 40 | 20 |
|                 | F   | 20           | 10           | 40 | 20 | 40 | 20 |
| 28 dpc         | M   | 20           | 10           | 40 | 20 | 40 | 20 |
|                 | F   | 20           | 10           | 40 | 20 | 40 | 20 |
| 55 dpc         | M   | 20           | 10           | 40 | 20 | 40 | 20 |
|                 | F   | 20           | 10           | 40 | 20 | 40 | 20 |
| Postnatal:      |     |               |               |   |   |   |   |
| 2 dpp<sup>d</sup> | M   | 20           | 10           | 40 | 20 | 40 | 20 |
|                 | F   | 20           | 10           | 40 | 20 | 40 | 20 |
| 70 dpp         | M   | 20           | 10           | —  | —  | 40 | 20 |
|                 | F   | 20           | 10           | —  | —  | 40 | 20 |
| 365 dpp        | M   | 20           | 10           | —  | —  | 80 | 40 |
|                 | F   | 20           | 10           | —  | —  | 80 | 40 |

<sup>a</sup> Animals scheduled to live out their life-span.

<sup>b</sup> Animals scheduled to be killed according to a sacrifice schedule at 5, 8, 11 or 14 years of age.

<sup>c</sup> Days postcoitus.

<sup>d</sup> Days postpartum.

Table 2. Exposure and dose statistics for Life-Span Study.

| Age at Exposure | Number Exposed | Exposure-R Mean (Range) | Absorbed Dose – cGy Mean (Range) | Mean Absorbed Dose for Major Exposure Groups (cGy) |
|-----------------|----------------|------------------------|-----------------------------------|-----------------------------------------------|
|                 |                |                        |                                   |                                               |
| Controls (all ages) | 359<sup>a</sup> | 0                      | 15.9 (15.4–16.4)                  |                                               |
| 8 dpc<sup>b</sup>    | 120            | 20.0 (17.1–22.0)       |                                   |                                               |
| 28 dpc             | 120            | 20.0 (17.4–21.4)       | 16.0 (15.4–16.9)                  |                                               |
| 55 dpc             | 120            | 20.0 (18.7–21.0)       | 15.6 (15.1–16.2)                  |                                               |
| 2 dpp<sup>c</sup>   | 120            | 20.0 (19.4–21.5)       | 17.5 (17.3–17.8)                  |                                               |
| 8 dpc              | 120            | 101.3 (93.2–119.3)     | 81.6 (74.6–92.6)                  |                                               |
| 28 dpc             | 120            | 101.3 (94.9–113.2)     | 80.8 (77.4–93.8)                  |                                               |
| 55 dpc             | 120            | 101.1 (91.0–107.9)     | 80.8 (75.3–90.0)                  |                                               |
| 2 dpp              | 120            | 101.5 (95.0–109.1)     | 88.3 (86.5–90.0)                  |                                               |
| 70 dpp             | 118<sup>b</sup>| 99.5 (92.5–111.5)      | 82.6 (81.3–83.9)                  |                                               |
| 365 dpp            | 231<sup>a</sup>| 100.0 (90.2–117.2)     | 81.2 (76.9–90.2)                  |                                               |

<sup>a</sup> Represents exclusion of 12 dogs which died prior to irradiation or sham-irradiation.

<sup>b</sup> Days postcoitus.

<sup>c</sup> Days postpartum.
Table 3. Malignant neoplasia as a cause of death in non-sacrifice life-span study dogs through 16 years of age at death.

| Treatment Age | Mean Dose (cGy) | Total No. of Animals/Group | Number of non-sacrifice Animals/Group | Number Dead through 16 years of age | Total No. Fatal Cancers | Malignant Lymphoma | Hemangiosarcoma | Mammary Carcinoma | Thyroid Carcinoma | Other Malignant |
|---------------|----------------|---------------------------|---------------------------------------|------------------------------------|-------------------------|-------------------|-----------------|------------------|------------------|-----------------|
| All           | 0              | 360                       | 276                                  | 254                                | 66                      | 16                | 5               | 16               | 2                | 27              |
| 8 dpc<sup>a</sup> | 16             | 120                       | 98                                   | 93                                 | 34                      | 9                 | 4               | 8                | 2                | 11              |
|               | 83             | 120                       | 98                                   | 95                                 | 32                      | 5                 | 8               | 6                | 0                | 13              |
| 28 dpc        | 16             | 120                       | 98                                   | 93                                 | 27                      | 11                | 2               | 4                | 0                | 10              |
|               | 83             | 120                       | 98                                   | 94                                 | 29                      | 6                 | 1               | 6                | 0                | 16              |
| 55 dpc        | 16             | 120                       | 98                                   | 97                                 | 33                      | 7                 | 4               | 5                | 4                | 13              |
|               | 83             | 120                       | 96                                   | 93                                 | 34                      | 11                | 6               | 4                | 0                | 13              |
| 2 dpp<sup>b</sup> | 16             | 120                       | 97                                   | 88                                 | 24                      | 3                 | 7               | 5                | 1                | 8               |
|               | 83             | 120                       | 97                                   | 92                                 | 37                      | 4                 | 2               | 6                | 0                | 25              |
| 70 dpp        | 83             | 120                       | 96                                   | 91                                 | 25                      | 8                 | 3               | 4                | 4                | 6               |
| 365 dpp       | 83             | 240                       | 191                                  | 185                                | 54                      | 12                | 6               | 6                | 2                | 28              |

Totals        | 1680           | 1343                      | 1275                                 | 395                                | 92                      | 48                | 70              | 15               | 170             |

<sup>a</sup> Days postcoitus.
<sup>b</sup> Days postpartum.
dry food and water ad libitum, and were observed daily and given regular veterinary clinical examinations. Various effects have been evaluated including, survival, growth and development, disease incidence patterns, and carcinogenesis. All dogs that lived their full life-span either died or were euthanatized due to terminal illness. Complete gross and histopathologic evaluations were performed on all dogs to determine the cause of death, identify diseases which contributed to death, and to diagnose any neoplasms. Neoplasms were recognized either clinically or at necropsy. Clinically-recognized neoplasms were removed surgically when feasible or were biopsied after detection. All pathologic data were entered into a computerized data base for storage and analysis.

The analysis of the incidence of neoplastic disease has been performed using the weighted combination of contingency tables described by Peto et al., (1980)\(^23\). Neoplasms were categorized according to the context in which they occurred; thus a neoplasm that was responsible for the death of the animal (fatal context) was categorized and analyzed differently than one found incidentally at necropsy (incidental context). Separate analysis of these groupings of tumors allowed for analysis of both carcinogenesis rates and the biologic impact (relative malignancy). Adjustment was made for competing risks of death as part of the analyses. The analyses for each age-at-exposure were performed using the pooled control group.

**RESULTS**

Prenatal and neonatal mortality was increased by the in utero radiation exposures as has been reported previously (Angleton et al. (1988)\(^22\)). Because of this and the fact that neonatal mortality was high in unexposed dogs, animals were entered into the life-span study at 14 days of age. Life-span and survival was then analyzed conditional on the fact that the dogs survived the first 14 days of life. Survival through 16 years of age was consistently and significantly lower for females, as compared with males, in all groups. There was an overall trend toward decreased survival in irradiated females as compared with controls in dogs given 83 cGy at 28 dpc (P<.01), 16 or 83 cGy at 55 dpc (P<.01), 83 cGy at 70 dpp (P=.05), and 83 cGy at 365 dpp (P=.08).

While there were a large number of primary neoplasms found in the study (over 10,000 primary neoplasms in the 1343 life-span dogs), this report will address only selected sets of data, including neoplasms which occurred early in life, those which were fatal and, in the case of thyroid gland, incidental tumors. While the study is complete, we have only analyzed the data through 16 years of age. This, however, is approaching the maximum life-span of the beagle and only 68 dogs exceeded this age. The data from those 68 dogs is unlikely to change significantly the patterns seen in the 1275 dogs reported here.

One of the early, and striking, findings was the occurrence of an unusual number of neoplasms in young (0–4 year-old) dogs irradiated in the perinatal period (55 dpc or 2 dpp) Benjamin et al. (1986)\(^24\)). Figure 1 shows the prevalence of early-occurring benign and malignant neoplasms in perinatally-irradiated dogs, in dogs irradiated at the two earlier and
two later exposure times, and in the controls. The great predominance of tumors (10 of 18 or 56%) occurred in dogs irradiated at 55 dpc (6/18 or 33%) and 2 dpp (4/18 or 23%). Of malignancies, 5/7 (71%) also were in the perinatally-irradiated groups. Furthermore, fatal cancers were seen only in the dogs irradiated in the perinatal period and all four deaths occurred prior to 2 years of age. These early fatal malignancies were a cerebral astrocytoma in a dog given 0.90 Gy at 55 dpc, a malignant lymphoma in a dog given 0.79 Gy at 55 dpc, a fibrosarcoma of the maxilla in a dog given 0.17 Gy at 2 dpp, and an oral squamous cell carcinoma in a dog given 0.89 Gy at 2 dpp. Considering that the perinatally-irradiated groups comprised only 28.6% of the experimental population this was an impressive finding. Table 4 summarizes the results of the statistical analyses relating to the occurrence of neoplasia. Analysis for positive trend with increasing dose indicated that both fatal malignancies and all neoplasms were statistically significantly increased in young dogs exposed as fetuses (55 dpc) or neonates (2 dpp).

Table 3 gives a summary of the major types of fatal neoplasms that were found in the irradiated and unirradiated dogs through 16 years of age. These are the raw numbers of fatal neoplasms and do not reflect time of appearance. Statistical analyses did take into account age-related incidence. Four types of neoplasms accounted for the majority of all fatal cancers. The most prevalent were lymphoid neoplasia and hemangiosarcomas, both of which were found in a variety of organs and tissues. The other two were carcinomas specific to the mammary gland and thyroid gland. The “other” category includes fatal tumors originating from a variety of organs and tissues, including but not limited to neoplasms of
the endocrine system (other than thyroid carcinoma), skin, respiratory tract, urogenital tract, and digestive system. While neoplasia was the single, most common cause of death in the study, other diseases did account for about two-thirds of all deaths. The most common non-neoplastic disease categories included chronic renal disease, cardiovascular diseases, hypothyroidism, idiopathic convulsive seizures (epilepsy), and inflammatory conditions.

The cumulative incidence for fatal malignancies in all dogs, pooling the age-at-exposure groups, is shown in Figure 2. There was an overall increase in fatal tumors in the irradiated groups. It is interesting to note that this increase was primarily in females (see Figures 3 and 4). Analysis for positive trend with dose (Table 4) for all fatal malignancies from 0-16 years indicated an increased risk after exposures early (8 dpc) and late (55 dpc) in gestation, in the neonatal period (2 dpp), and in the young adult (365 dpp). It should be noted that the strongest and most significant trend was still in the dogs irradiated in the perinatal period. It also should be noted that in the two age-at-exposure groups that did not show a statistically significant increase in fatal cancer risk, the trends were still positive for increasing risk with increasing dose (28 dpc, P=.25; 70 dpp, P=.28). Figures 5 and 6 show the cumulative incidence of fatal malignancies in dogs irradiated at 55 dpc and 2 dpp, respectively. The earlier appearance of fatal cancers which are evident in these two experimental groups has already been noted.

Fatal malignancies of the lymphohematopoietic system (malignant lymphoma) were a leading cause of death in this study. This complex included lymphomas in a variety of organs, most often in a generalized form, and included lymphoid leukemias. In our dogs,
Fig. 2. Cumulative incidence of fatal malignancies in all dogs grouped by radiation dose. All ages-at-exposure are combined.

Fig. 3. Cumulative incidence of fatal malignancies in male dogs grouped by radiation dose. All ages-at-exposure are combined.
Fig. 4. Cumulative incidence of fatal malignancies in female dogs grouped by radiation dose. All ages-at-exposure are combined.

Fig. 5. Cumulative incidence of fatal malignancies in dogs irradiated at 55 days postcoitus (late fetal period). Males and females combined.
most of these appeared as an acute disease syndrome with a relatively short course. Studies with specific immunologic markers indicated that most were of B cell origin. Figure 7 shows the cumulative incidence of lymphoma in dogs irradiated at 55 dpc, the only group in which there was a statistically significant increase (see Table 4). Once again, an earlier appearance of fatal lymphoma was evident in the irradiated dogs.

Hemangiosarcomas of a variety of organs were common in study dogs. Dogs irradiated at 8 dpc or 55 dpc had an increased risk for fatal hemangiosarcomas (Table 4). Figure 8 shows the cumulative incidence of fatal hemangiosarcoma in dogs irradiated at 55 dpc. An earlier appearance of fatal hemangiosarcomas was seen in irradiated animals.

Thyroid adenocarcinoma as a cause of death was increased only in dogs irradiated in the juvenile period at 70 dpp (Table 4). Figure 9 shows the cumulative incidence of fatal thyroid carcinoma in this groups. The higher incidence and the earlier appearance of these tumors is evident. Incidental thyroid neoplasms, both benign and malignant, were also increased in irradiated dogs, again only in those irradiated at 70 dpp. This increase was statistically significant (P<.01). For both fatal and incidental thyroid tumors, both sexes were equally affected (Figure 10).

The neoplasms classified under “other” fatal malignancies represent an intriguing category. While there were too few of any one type to analyze as individual tumors, there was a distinct trend for increased risk with increasing dose in all but one (70 dpp) of the age-at-exposure groups (Table 4). One group of neoplasms in this category represents an important subset for evaluation. Myeloproliferative disorders are a general category of bone marrow proliferative disorders that encompass a spectrum from myeloid hyperplasia through frank leukemia. These are rare spontaneous diseases in the dog but are highly sensitive to

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Fig. 6. Cumulative incidence of fatal malignancies in dogs irradiated at 2 days postpartum (neonatal period). Males and females combined.
Fig. 7. Cumulative incidence of fatal lymphoid neoplasia in dogs irradiated at 55 days postcoitus (late fetal period). Males and females combined.

Fig. 8. Cumulative incidence of fatal hemangiosarcomas in dogs irradiated at 55 days postcoitus (late fetal period). Males and females combined.
Fig. 9. Cumulative incidence of fatal thyroid carcinomas in dogs irradiated at 70 days postpartum (juvenile period). Males and females combined.

Fig. 10. Cumulative incidence of incidental thyroid neoplasia in dogs irradiated with 83 cGy at 70 days postpartum (juvenile period).
induction by ionizing radiation. In our study, there were five cases of myeloproliferative disorders, including three frank myeloid leukemias; one dog received 16.1 cGy at 28 dpc, one dog received 15.7 cGy at 55 dpc, one dog received 17.5 cGy at 2 dpp, and two dogs received 88.0 and 89.5 cGy, respectively, at 2 dpp. No cases were seen in any other groups including the controls.

Surprisingly, there was no evidence of an increased risk for mammary carcinoma after irradiation at any age-at-exposure. There were several sub-types of mammary carcinoma which had differing degrees of malignant and metastatic potential. Final analyses will need to evaluate whether risk for specific sub-types might be affected by radiation exposure.

DISCUSSION

The data presented suggest a number of conclusions. First, it appears there is an increase in both benign and malignant, especially fatal malignant, neoplasms in young dogs after perinatal irradiation (Benjamin et al. (1986)\textsuperscript{24}). Because the number of neoplasms was relatively small in this group, it is useful to compare the findings in our dogs to those of the general canine population. The most comprehensive canine data (Priester et al. (1980)\textsuperscript{25}) indicate the rate for malignant tumors in all breeds of dogs from 0 to 2 years-of-age in 335 cases/238,994 animal-years-at-risk or 1.53/1,000. In our study, the rate for malignant tumors in perinatally-irradiated dogs from 0 to 2 years of age is 4 cases/943 animal-years-at-risk or 4.24/1,000. While this is more than three times higher than the spontaneous rate in the canine, more impressive is the fatality rate. Priester et al. estimated that only 21.5\% of the malignancies seen had metastasized. Not all tumors that metastasize are fatal and tumors that do not metastasize can also lead to death. Even so, if we assume that 25\% of all spontaneous malignancies seen in young dogs of all breeds cause death, this translates to a fatality rate of 0.38/1,000 animal-years-at-risk, a rate tenfold less than that seen in perinatally-irradiated dogs in our study.

A second tentative conclusion from the data presented is that both prenatal and postnatal irradiation are associated with an increased risk for neoplasia in later life. It may be important that a trend for an increased risk for all fatal malignancies, although statistically significant in only four of six experimental groups, was noted across all ages-at-exposure. Further, if one looks at the "other" category of neoplasms, a subgroup which is larger than any of the four major neoplasm types, there again is evidence of increased risk across most age-at-exposure groups. While, from this, the dog might appear to have a generally high sensitivity to radiation carcinogenesis, there is little question that this trend is most pronounced in dogs irradiated in the perinatal period, considering both the heightened responses in the young dogs and the greater degree of response throughout the life-span.

The occurrence of thyroid neoplasia in our study, while not related to perinatal exposure, is consistent with the findings in humans which indicate that susceptibility to radiation-induced thyroid cancer is greatest in early childhood (Shore et al. (1985)\textsuperscript{26}, Ron et al. (1989)\textsuperscript{27}, BEIR (1990)\textsuperscript{28}). In the dog, as in humans, both benign and malignant thyroid
neoplasms resulted after radiation exposure.

Because the tumorigenic response does show across so many exposure ages, it might be suggested that this is simply because the fatal cancer rate in the control dogs is artificially low. This case is not supported by the data on the earlier times to death in irradiated dogs with all fatal malignancies, including those in the young dogs (Figures 5 and 6). While the numbers of tumors are smaller for each of the major individual types of neoplasms, in each case examined there was not only increased risk after irradiation, but also an advancement in the time of occurrence of the fatalities, i.e., a shortening of the latent period. This appears to strengthen the impact of the findings. A control population with a fatal cancer rate which was low due to chance should not result in such a consistent finding across tumors types with respect to latent period.

The interpretation of epidemiologic data to infer that the human fetus has a relatively high sensitivity to radiation carcinogenesis has often been challenged based on a purported lack of such prenatal sensitivity in experimental animals (BEIR (1990)28)). There have been numerous studies of age-related sensitivity using external radiation exposure and internally deposited radionuclides in a variety of animals, primarily rodents (reviewed in Sikov (1981, 1989)18,19)). Studies have demonstrated both increases and decreases in specific neoplasms after prenatal or neonatal exposures, however, this must be considered in light of several factors. First, there are clearly differences in sensitivity between species and strains of animals used. Second, both dose and the specific time of irradiation with respect to gestation can influence tumorigenic responses. Third, whether animals are killed at predetermined times or allowed to live out their full life-spans can influence the tumorigenic endpoint being evaluated. Finally, relatively few studies have compared concurrently the oncogenic susceptibility of animals exposed as fetuses and as adults.

Those studies which have compared animals exposed in the fetal and postnatal periods are enlightening. Upton et al. (1960)29) reported that myelogenous leukemia was increased in mice irradiated as adults, but not in those irradiated as fetuses. This work has often been cited as evidence against existence of a heightened fetal radiosensitivity. Other studies in mice also have shown a lack of leukemogenic response after fetal irradiation (Schmahl (1984)30), Schmahl (1988)31)). Reductions in the incidence of neoplasms of the reticulum cell sarcoma/histiocytic lymphoma type in mice have also been reported after fetal irradiation (Covelli et al. (1984)32), Sasaki et al. (1986)33)). What must be recognized, however, is that in some of the same experiments the fetus was shown to be more sensitive to radiation-induced tumors of a variety of other organ systems, including lung, liver, and pituitary gland (Sasaki et al. (1986)33), as well as other solid tumors (Covelli et al. (1984)32), Walinder (1984)34), Sasaki et al. (1986)33)). It also should be noted that decreased tumor incidence was often the result of high dose radiation exposure in the fetal period. While, in some cases, this decreased tumor incidence may have related to overall life shortening (Sikov (1981)18)), a number of studies have noted that the fetus actually shows no greater (Covelli et al. (1984)32) or a lesser sensitivity (Sasaki et al. (1986)33)) to life shortening than the adult.

A few rodent studies also have addressed differences in sensitivity between the fetus and the neonate and the neonate and the adult. In some studies carcinogenic responses
were similar between fetal and neonatal exposures (Upton et al. (1960)\textsuperscript{29}, Kasuma et al. (1982)\textsuperscript{35}). Data from other studies suggested that the neonatal sensitivity of the mouse was actually greater than that of the fetus or the adult, at least for some neoplasms (Sasaki et al. (1978, 1986)\textsuperscript{36,33}, Covelli et al. (1984)\textsuperscript{32}). Some organs, like the pituitary gland, show the highest sensitivity in the fetus (Sasaki et al. (1986)\textsuperscript{33}, Schmahl et al. (1981)\textsuperscript{37}).

The dog, specifically the beagle, has been used widely for research on the effects of radiation. Most studies have involved exposures to high doses of external radiation, to chronic irradiation, or to internally-deposited radionuclides with low or high LET emissions. Few studies have addressed the question of prenatal exposures. Beagles exposed to chronic \textit{\textsuperscript{60-Co}} gamma radiation (11 R/day), starting at either 21 days of gestation or 50 to 150 days after birth, had a dramatically higher risk for myeloproliferative disorders in the group initially irradiated as fetuses (Stitzel et al. (1982)\textsuperscript{38}). Also, after irradiation starting in the fetal period, dogs were able to survive much higher radiation doses, a response akin to the increased survival in some fetally-irradiated rodents. Seed et al. (1987)\textsuperscript{39} chronically irradiated beagles with \textit{\textsuperscript{60-Co}} (7.5 cGy/day) during the fetal period only, both fetally and postnatally, or postnatally only. They found that continuous chronic irradiation over a long time period was a more important determinant of myeloid leukemogenesis, than whether the exposure started in the fetal or postnatal period. They did note a change in radiosensitivity with age from birth to young adulthood, with dogs becoming less radiotolerant resulting in shorter survival and fewer dogs at high risk for leukemia. It is noteworthy that all the cases of myeloproliferative disorders seen in our study were in dogs exposed in mid-to-late gestation or as neonates. Priester et al. (1980)\textsuperscript{25} reported that the occurrence of all non-lymphocytic leukemias (including “miscellaneous” and unspecified types) was 94 cases/523,706 animal-years-at-risk or 0.18/1,000. In our dogs irradiated at mid or late gestation or as neonates, the myeloproliferative disorder/leukemia rate was roughly 0.75 cases/1,000 animal-years-at-risk, four times the ‘spontaneous’ rate. Further, the spontaneous rate is likely to be overstated because of the inclusion of unspecified leukemias. These data suggest a radiogenic origin our cases.

In a recent review, MacMahon (1989)\textsuperscript{40} states that the relative sensitivity of the fetus to radiation carcinogenesis is still an extant issue. He again raises the question of evidence from animal studies, stating that there is no obvious reason why the susceptibility of the human to radiation should suddenly change at birth. Data from our studies reported here suggest that the period both before and after birth have a heightened responsiveness, and similar data from some of the rodent studies noted above suggest that such a dramatic change does not take place at birth in many animal models. Sikov (1981)\textsuperscript{18} even suggested that the neonatal rodent might be a better model for human fetal carcinogenesis, presumably because of the differences in the developmental stages at birth. Another long-standing objection to the idea of a causal relationship between prenatal irradiation and childhood cancer is the fact that in prenatally-exposed infants both the leukemias and all the major groups of solid tumors are increased almost equally, “a situation quite uncharacteristic of any other human or animal exposure” (MacMahon (1989)\textsuperscript{40}). While the data in our dogs are, as yet, not completely analyzed, there does appear to be evidence of an increase in a
broad spectrum of neoplasms, including both leukemia and a variety of solid neoplasms.

In conclusion, the data from the studies of radiation carcinogenesis during development would suggest that the dog shows a generally heightened sensitivity to radiation when exposed in the perinatal period. This is manifested as an increase in both all tumors in young dogs (less than 4 years of age), and in fatal cancers in very young dogs (less than two years of age) and in aging dogs (up to 16 years of age). These data are similar to those which have been reported for the human population and support a continuing concern for prenatally irradiated people.

ACKNOWLEDGEMENTS

The authors thank the staff of the Collaborative Radiological Health Laboratory for their assistance in carrying out this research. In particular, we thank Mary Englund and Margaret Miller for administrative support and manuscript preparation, David Farris and Kathleen Peterson for data management and analysis, and Laura Chubb for technical and graphics support.

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