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239 Pu in Dogs

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Pathology of Irradiation

edited by

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Some Toxicity Aspects of Internally Deposited Plutonium-239

G. N. TAYLOR, T. F. DOUGHERTY, AND W. R. CHRISTENSEN

INTRODUCTION

Plutonium-239 is a good example of a radionuclide which is retained within the body for prolonged periods, and thus irradiates selected organs or specific tissues within an organ with relatively high energy (5.14 mev) alpha particles.¹⁻¹⁰ The range of a ²³⁹Pu 5.14-mev alpha particle is approximately 35 μ in soft tissue and 25 μ in compact bone.¹¹ Plutonium's behavior also typifies the complex problems encountered in the study of internal radiation. For example, the deposition pattern is markedly influenced by the route of entry into the body, the physical and chemical states of the radionuclide before and after exposure, the age and metabolic state of the organism at the time of exposure, and species differences—just to mention a few of the variables.

Further complexities arise from the ever-changing tissue concentration and unequal distribution patterns of the radionuclide within a given tissue or organ. Also, the specific target cell is frequently unknown. Thus, the precise local dose for a given response is seldom known. In some instances the dosimetry is further complicated by the continuous movement of cells into or away from the radiation field. Also, precise latent periods for the various lesions are usually difficult or impossible to determine, since the lesion is usually not detected until sometime after the injurious dose was received. Thus, the induction dose is usually significantly less than the accumulated dose at the recognition time of the lesion. These factors are just a few of the variables involved in evaluating the effects of internally deposited radionuclides on the

components of a dynamic biologic system and suffice to emphasize some of the problems encountered and the potential variability in the toxicity syndromes induced by the respective radionuclides or various physical and chemical states of the same radionuclide. Thus, the toxicity syndrome of ²³⁹Pu in a dog, as presented in this study, is not given as a typical example of internal radiation but as a specific case indicating some of the major end-points induced by one of the more important and very toxic radionuclides. Nevertheless, it does serve to indicate some of the more general factors involved in the study of internal radiation.

METHODS

All of the animals summarized in this study were pure-bred beagles which were progeny from a moderately inbred colony.¹² They were maintained under disease-free conditions, and environmental, dietary, and general animal care factors were comparable for each animal throughout its life span.

The plutonium was administered in the tetravalent form, in a citric acid sodium citrate buffer (pH 3.5) via a single intravenous injection, at approximately 16 to 17 months of age.¹² All of the epiphyses were closed at this time, except those of the costochondral junction. The animals were kept until death or were sacrificed when death was imminent. The dose levels and numbers of dogs observed are shown in Table 7.1.

The percentage fractures (shown below in Fig. 7.6) were based on the total number occurring in a specific bone, as related to the total number of these bones pres-

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TABLE 7.1
Injection Dose Levels

Dose Injected	No. of Long-Term Dogs
$\mu\text{C per kg b. wt.}$	
0.0158	13
0.0474	13
0.0948	12
0.284	12
0.853	12
2.8766	21

ent in the given number of dogs at the respective dose levels. The fractures shown for the thoracic vertebrae were limited entirely to the dorsal spinous processes and those for the lumbar vertebrae involved both dorsal spinous and transverse processes.

The induction times for the osteosarcomas are the intervals from injection of ^{239}Pu to the time of death and not the time of first recognition.

The autoradiograms are from acetone-fixed tissues, prepared according to the method of Arnold and Jee.¹³

RESULTS

Following a single intravenous injection of tetravalent ^{239}Pu , most of the retained radionuclide burden was ultimately localized in the skeleton (approximately 60%) and the liver (approximately 30%), where it was retained for prolonged periods.^{7,8} Much less significant deposition sites were the thyroid,¹⁴ the kidney, and the spleen.^{7,8} Thus, these and the immediately adjacent tissues, such as the bone marrow, were the principal target organs. The following observations summarize the most significant aspects of the toxicity syndrome.

Hematopoietic Changes

The earliest clinically detectable radiation-induced change was a drop in the leukocytes of the peripheral blood.¹⁵ The depression was most acute at the 2.8 $\mu\text{C per kg}$ dose and became minimal or nonsignificant below 0.095 $\mu\text{C per kg}$. Partial recovery occurred at various post-injection times, which varied according

to the injected dose level. In spite of the very significant blood dyscrasia, death due to hematopoietic changes did not occur and hematopoietic neoplasms were not induced.¹⁶

Liver Disease

Approximately 25% of the dogs injected at the highest level died with primary plutonium-induced liver disease, beginning at approximately 400 days post-injection. In the cases of primary liver disease, the liver at death was one-half to one-third normal weight and severe secondary portal hypertension was invariably present. The earliest evidence of hepatic injury was a significant elevation in the serum glutamic pyruvic transaminase which occurred approximately 200 days post-injection at the highest dose.¹⁷ The hepatic syndrome indicated that the 3 $\mu\text{C per kg}$ dose of ^{239}Pu appeared to be very near the LD_{50} for the dog, with death due to subacute primary liver disease at post-injection times greater than 400 days. Significantly higher doses would

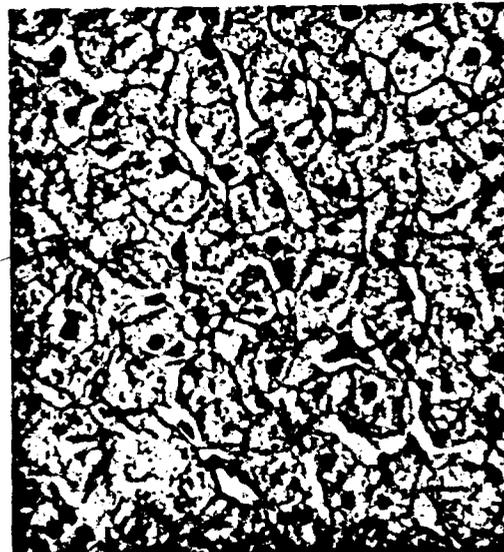


FIG. 7.1. Autoradiogram of 6- μ section of beagle liver taken 13 days following a single intravenous injection of 2.4 μC of ^{239}Pu per kg which shows a uniform distribution of alpha tracks (arrow) arising from the hepatic epithelium. Exposure, 27 days. $\times 380$.

undoubtedly lead to more acute deaths from hematopoietic factors.

Initially, the ^{239}Pu was uniformly distributed throughout the hepatic cells and was strikingly absent from the reticuloendothelial (RE) and portal tissue, including the biliary epithelium (Fig. 7.1). This pattern persisted until approximately 200 to 300 days post-injection, after which a significant translocation of the ^{239}Pu to the RE cells produced prominent "hot spots" (Fig. 7.2). Eventually, a high percentage of the radionuclide was localized in the individual RE cells lining the sinusoids, especially at the highest dose levels. The formation of the first hot spots coincided with the earliest rise in SGPT and was probably the result of increased liver necrosis. The rate of movement into the RE cells appeared to be a function of the degree of injury to

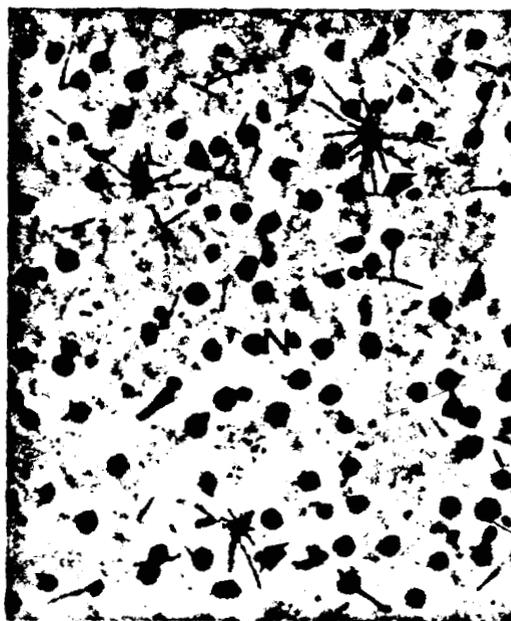


FIG. 7.2. Autoradiogram of 6- μ section of beagle liver taken 362 days following a single intravenous injection of 0.303 μC of ^{239}Pu per kg which shows the early translocation of the radionuclide to the RE cells (arrow). Also shown are foci of relatively nonradioactive parenchymal cells (N). Exposure, 47 days. $\times 380$.

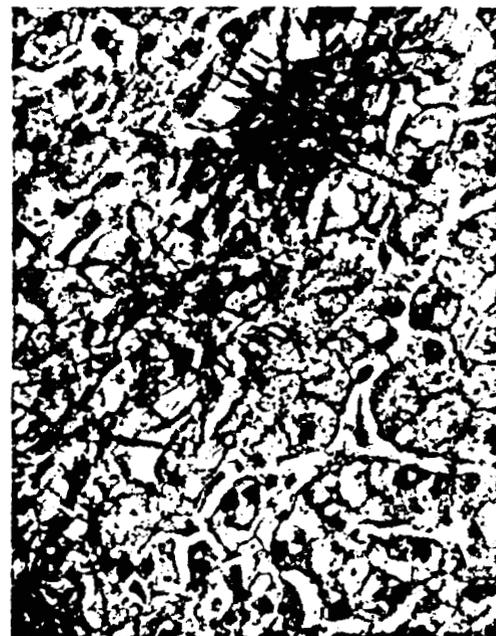


FIG. 7.3. Autoradiogram of 6- μ section of beagle liver taken 1,400 days following a single intravenous injection of 2.91 μC of ^{239}Pu per kg showing the aggregation of a high percentage of the plutonium in the portal areas, which occurs at relatively long post-injection times. Exposure, 27 days. $\times 380$.

the hepatic parenchyma and was greatest at the highest dose levels.

A distinctive feature in the translocation of ^{239}Pu to the RE cells was its association with iron-staining pigments, presumably hemosiderin. The ^{239}Pu in liver cells other than the hepatic epithelium was seldom observed in the absence of such iron-staining material and appeared to be bound to this compound. Following the shift of ^{239}Pu and the associated iron pigment to the RE cells, a further translocation to the stromal areas, including the subcapsular regions, occurred until ultimately a high percentage of the ^{239}Pu retained in the liver was localized in these areas (Figs. 7.3 and 7.4). This feature was most obvious and occurred at shorter post-injection times at the highest levels. Again, the alpha activity was invariably associated with iron-staining pigment and a high percentage was still retained within

macrophages, which presumably served as transport vehicles from the more central areas. This movement to the stromal areas was obviously quite efficient, since the plutonium was lost from the liver at a very slow rate.⁷

The plutonium distribution pattern was also influenced by regenerative changes. This was principally a mechanical displacement of the older radioactive tissue by foci of younger regenerating hepatic cells of very low plutonium activity (Fig. 7.5). These changes were prominent even at the lowest dose level, 0.015 μC per kg, but only after relatively long latent periods. Such regenerative changes represented a replacement phenomenon since the liver weight usually remained normal even though 70 to 80% of the liver was eventually composed of regenerative



FIG. 7.5. Microphotograph showing numerous foci of regenerating hepatic cells (R) in a beagle liver 3,430 days following a single intravenous injection of 0.0495 μC of ^{239}Pu per kg. Unstained formalin-fixed specimen. $\times 134$.

TABLE 7.2
Summary of Primary Liver Tumors Observed
in ^{239}Pu -Treated Dogs

No. of Tumors	Dogs at Risk	Percent Incidence	Ave. Age at Neoplasia yrs	Range of Neoplastic Dose Levels $\mu\text{C } ^{239}\text{Pu per kg}$
7 ^a	35 ^b	20	13 (9-14) ^c	0.0139-0.0968

^a All tumors were intrahepatic bile duct type.

^b Includes only dogs 8 years or older.

^c Range.



FIG. 7.4. Autoradiogram of 6- μ section of liver showing the late localization of plutonium in the subcapsular areas. Same dog as Figure 7.3. Exposure, 27 days. $\times 380$.

tissue. In spite of the very marked liver changes, fibrosis did not occur.

A third factor in the plutonium-induced liver syndrome was a moderate number of primary liver tumors which occurred in the long-term low level animals. Table 7.2 summarizes the incidence observed thus far.

All of the tumors were the bile duct type. Only two were the primary cause of death with the others being quite small and found incidentally at autopsy.

Fractures

Another feature of plutonium toxicity was the induction of pathologic fractures. These occurred in the three highest dose levels: 2.8, 1, and 0.3 μC per kg (Fig. 7.6). The earliest fracture was observed approximately 390 days post-injection, with an average skeletal dose of 3,180 rads.¹⁸ The incidence dropped sharply between 2.8 and 1.0 μC per kg doses and became

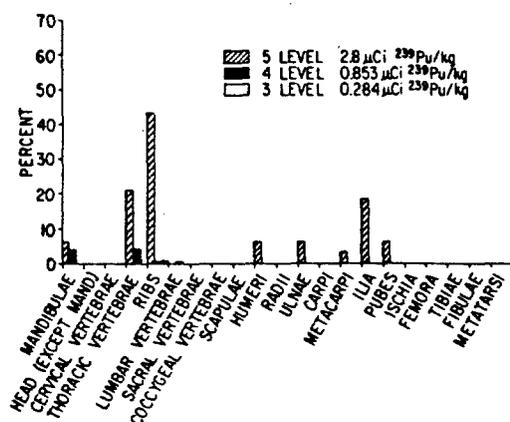


FIG. 7.6. Anatomical distribution and percent incidence of pathologic fractures in dogs following a single intravenous injection of ^{239}Pu .

insignificant at the $0.3 \mu\text{C}$ per kg dose level. A significant percentage healed normally when they were properly immobilized.

In spite of other very obvious radiographically apparent changes, the fracture sites usually could not be predicted by radiography. This was in agreement with strength tests of defleshed bones which established that ^{239}Pu -induced changes in the breaking stress were not sufficient to account for the pathologic fractures and the etiology was tentatively ascribed to the induction of localized bone faults.¹⁹

A unique feature of these radiation-induced fractures was the minimal amount of pain associated with them.

Tooth Loss

An abnormal rate of tooth loss was first observed at the $0.0948 \mu\text{C}$ per kg dose level and the rate increased with each successively higher dose (Fig. 7.7). The dental lesions, which ultimately resulted in tooth loss, were clearly separable from the naturally occurring nonradiation factors such as the periodontal syndrome and were similar to those induced by other bone-seeking radionuclides, such as radium and radiothorium. The lesions, as seen radiographically, were characterized

by loss of the periodontal ligament, ankylosis of the roots, unique dental caries, and exfoliation of the crowns in the advanced cases (Figs. 7.8 and 7.9). Varying degrees of root resorption occurred prior to, but especially after, the loss of the crowns.

Marked lesions in the adjacent bony structures occurred concurrently with the tooth changes. Radiographically these were seen as coarsening and loss of spongy bone and formation of radiolucent foci in the mandibular cortex, especially at the higher dose levels. Dental radiography was the most sensitive *in vivo* method of detecting non-neoplastic plutonium-induced skeletal injury. Within general limits it was possible to determine the dose level by examination of the dental occlusal films.

Turbinate Atrophy

In addition to the fractures and bone tumors, an additional very obvious plutonium-induced bony change was turbinate osteolysis (Figs. 7.10 and 7.11). This was marked at the higher dose levels and occurred to a lesser degree down to levels as low as $0.5 \mu\text{C}$ per kg. In the lower doses it was frequently the only non-neo-

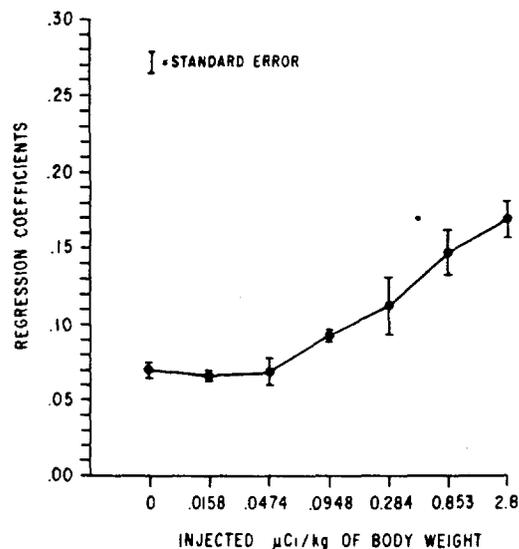


FIG. 7.7. Comparison of the regression coefficients for rate of tooth loss in beagles injected with ^{239}Pu .

ligament, ankylotic changes, dental caries, and the advanced varying degrees of osteolysis prior to, but adjacent bony structures currently with radiographically evident loss of radiolucency of the cortex, especially the maxilla. Dental radiographs are sensitive *in vivo* to neoplastic injury. Within the limits of the technique available to determine the extent of the

plastic skeletal lesion that was obvious during the gross postmortem dissection. Thus far, primary neoplasms have not occurred at this site and the osteolysis did not produce serious clinical problems. The apparent atrophy resulted from varying degrees of osteolysis involving the thin, bony laminae which formed the framework of this structure. In some of the highest levels, complete loss of the bone occurred. Changes in the overlying mucous membrane were not remarkable.



FIG. 7.8. (Top.) Radiograph of left mandible of 592-day-old beagle showing normal bone and dental morphology. $\times 2\frac{1}{2}$.

FIG. 7.9. (Bottom.) Radiograph of left mandible of beagle 1,338 days following a single intravenous injection of $0.838 \mu\text{C}$ of ^{239}Pu per kg showing dental caries, root resorption, loss of the periodontal ligament, and marked coarsening of the spongy bone of the alveolar crests. Same dog as Figure 7.8. $\times 2\frac{1}{2}$.



FIG. 7.10. (Top.) Photograph of midsagittal section through beagle skull with nasal septum removed showing the normal appearance of the maxilloturbinate and ethmoturbinates (arrows). $\times 1\frac{3}{4}$.

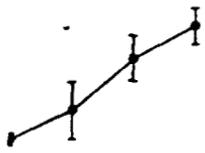
FIG. 7.11. (Bottom.) Photograph of midsagittal section through beagle skull 1,400 days following injection of $2.91 \mu\text{C}$ of ^{239}Pu per kg showing marked involution of the maxilloturbinate and ethmoturbinates (arrows). $\times 1\frac{3}{4}$.

Similar lesions were seen in the ethmoid labyrinth but were less obvious grossly. The identical syndrome also occurred in dogs treated with other bone-seeking radionuclides such as ^{226}Ra , ^{228}Ra , and ^{228}Th . It was not observed in animals treated with relatively high doses of beta-emitting ^{90}Sr .

Bone Tumors

The leading cause of death following intravenous injection of tetravalent ^{239}Pu was the induction of osteosarcomas.^{20, 21} Thus far such tumors have occurred as low as the $0.0158 \mu\text{C}$ per kg dose level

structures and bone density. A very obvious plunge was observed (Fig. 7.11). This was at the dose levels and was down to levels observed in the lower dose only non-neo-



348 0.284 0.853 2.8

OF BODY WEIGHT
regression coefficients
injected with ^{239}Pu .

and at an average cumulative skeletal dose as low as 60 rads. Since the cumulative rad dose was based on the survival time, the tumor-induction dose was less than this. However, the local dose to the critical cells, because of the surface deposition, was much higher than the average skeletal dose. The average length of time from injection until death from osteosarcoma generally increased as the dose was lowered; however, the range of the survival times for some of the injected dose levels overlapped significantly (Fig. 7.12). The anatomical distribution of such neoplasms was more generalized than described for the nonradiation-induced bone tumors observed in other canine breeds.²²⁻²⁴

The spontaneous osteosarcoma incidence in the beagle is very low and lies somewhere between 1 to 100 cases per 100,000 deaths.²⁵ Thus it is fairly certain that all the tumors presented in this study were radiation-induced.

Secondary Lesions

In general the plutonium lesions were localized within the focally irradiated areas. However, several conditions developed which may have been secondary to the overall radiation effect. Some of these, especially the decreased longevity

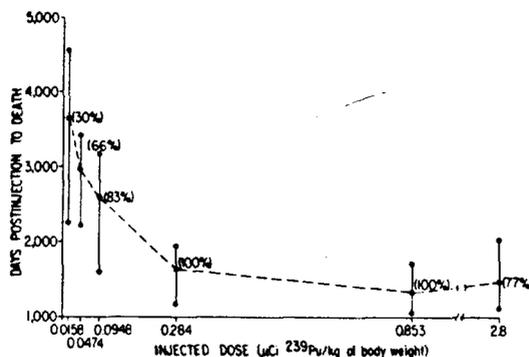


FIG. 7.12. Average osteosarcoma latent period of beagles receiving a single intravenous injection of ^{239}Pu . The range of the latent period is designated by the vertical bars and the percent incidence is shown in parentheses.

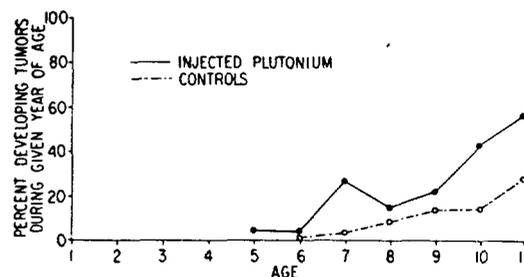


FIG. 7.13. Age-specific soft tissue tumor incidence in control and ^{239}Pu -treated dogs. (Does not include ^{239}Pu -induced liver tumors.)

and the increase in soft tissue tumors, may have resulted from the relatively small sample size. Their relationship to plutonium toxicity is not conclusive. Four conditions which have been tentatively considered to be secondary are as follows:

Lymphopenia. This occurred consistently at the higher levels even though the lymphatic tissue, other than that associated with the bone marrow, was not irradiated to a significant degree.²⁶

Lymphatic Hyperplasia. This occurred in the lymph nodes of a few of the dogs injected at the 0.015 to 0.045 μC per kg dose levels. It developed only after relatively long latent periods and was not seen in the controls.

Increased Incidence of Soft Tissue Tumors. The incidence of soft tissue neoplasms in the irradiated dogs, excluding the unequivocally radiation-induced tumors, was moderately higher than the controls (Fig. 7.13).

Decreased Longevity. The life span of the lowest dose level (0.015 μC per kg) in which a significant number did not die of clearly established plutonium toxicity was approximately 15% below their controls.

DISCUSSION

Although plutonium produced very significant non-neoplastic changes at the relatively high dose levels, the most universal and serious threat was bone cancer. A high incidence occurred at all of the dose levels studied and thus far has de-

veloped at injection levels $\frac{1}{16}$ of the fracture-induction dose and a factor of six below the dose level which produced accelerated tooth loss or detectable hematopoietic changes.

The unusually high carcinogenic activity of ^{239}Pu was principally related to its selective deposition on bone surfaces (Fig. 7.14). In the skeleton the plutonium was in close proximity to the osteogenic tissue and presumably adjacent to the most sensitive cells from the standpoint of neoplasia. The enhanced toxicity of this surface deposition was especially obvious by intercomparison with an alpha-emitting bone-seeking radionuclide, such as ^{226}Ra , in which the distribution was more uniform throughout the volume of

the skeleton. Such a comparison indicated that ^{239}Pu was five to ten times more effective in the induction of osteosarcomas.²¹

The relatively low incidence of liver tumors was unexpected in view of the marked regenerative changes which occurred even at the lowest injected dose. Although the liver was highly radiosensitive with respect to the regenerative changes, the susceptibility to neoplasia was much less than the skeleton rad for rad. This was possibly the result of a shorter latent period in the case of the osteosarcoma and thus earlier death from bone cancer. It also may have been related to significant differences in the local dose rate. The shortest post-injection time for a liver tumor was 2,777 days and the average was 3,587 days.

The absence of hepatic hemangioendotheliomas was also significant, especially since this was such a common endpoint in thorotrast cases with high liver burdens. Failure of such tumors to appear in the experimental animals of this study lends considerable support to the thesis that the thorotrast-induced hemangioendotheliomas may not be radiation-induced.²⁷

In spite of the relatively low incidence of liver tumors, it is significant that they did occur down to the lowest level in which bone tumors were observed and this end-point must certainly be considered as a factor in plutonium toxicity. In man, the hepatic concentration of ^{239}Pu is significantly higher relative to the skeleton following chronic inhalation exposure, and liver neoplasms may be a more important end-point than has been observed in animal experiments such as these.²⁸⁻³⁰

Probably the most important finding to emerge from a study such as this would be the maximum permissible body burden that could be tolerated without significant harm to the organism. In most instances this involves the study of very low dose levels and thus requires large numbers of animals and tedious life span observations. For these and other reasons it



FIG. 7.14. Autoradiogram of bone trabecula (T) from a beagle showing the surface deposition pattern of plutonium 14 days following a single intravenous injection of 0.949 μC of ^{239}Pu per kg. Exposure, 21 days. $\times 360$.

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is tempting to make extrapolations from higher dose levels; however, this is open to serious error. For example, in the case of the human radium studies, there is evidence of a practical threshold.³¹ Also, entirely different end-points may appear at the lower levels which could not be predicted by extrapolation. This occurred in long-term canine radium studies in which radiation-induced intraocular melanomas occurred as an important late effect only at the lower dose levels.¹⁶ Presently in the evaluation of the toxicity of internal irradiation, there does not appear to be a satisfactory alternative to long-term life-span studies which include a significant number of animals at relatively low dose levels.

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