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PHYSIOLOGY AND TOXICOLOGY OF PLUTONIUM-239 AND ITS INDUSTRIAL MEDICAL CONTROL*

W. H. LANGHAM

Los Alamos Scientific Laboratory, University of California,
Los Alamos, New Mexico

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Abstract—When taken into the systemic circulation, Pu^{239} deposits predominantly in the skeleton, where it may produce bone disease (including cancer) many years later. Its absorption rate from the gastrointestinal tract is only about 0.003 per cent. A small amount may be absorbed through the intact skin and through contaminated cuts and puncture wounds. Absorption from the lung may be from 1 to 10 per cent of the inhaled dose, depending on particle size, solubility, chemical form, etc. Inhalation of contaminated air is potentially the most important mode of exposure, and its control is largely responsible for the rigorous closed-systems and other industrial hygiene and engineering practices employed in plutonium processing. Once in the body, Pu^{239} is excreted extremely slowly (about 200 years being required to eliminate one-half the body burden). An individual who has reached the maximum permissible body burden technically should be removed from further plutonium contact for the rest of his life. The maximum permissible body burden of Pu^{239} (0.04 μc) is established by comparison with Ra^{226} and is that amount which has the same improbability of producing harm to any person at any time during his natural life as does 0.1 μc of fixed Ra^{226}.

Control of the industrial hazards of Pu^{239} processing is based on the premise that exposure of personnel should be as nearly zero as possible. This is not because less than the maximum permissible body burden is apt to do harm, but because it is sound industrial medical and economic practice. If presently recommended practices are maintained, there is little reason to feel that the health of a person working with Pu^{239} will be subject to any greater absolute risk than if he were engaged in any other chemical or industrial occupation.

INTRODUCTION

DURING the past 15 years, processing of Pu^{239} has grown from novel microtechniques applied by a few individuals into a routine industrial procedure involving many people and kilogram quantities of material. Concurrent with the growth of the industry has been a progressive realization that the most effective control of the industrial medical problems of plutonium processing is through the adoption of rigorous and elaborate industrial engineering measures such that exposure of operating personnel is as nearly zero as possible. This emphasis on minimal exposure conditions, unless viewed in context with the toxicological and physiological properties of plutonium, may cause unwarranted apprehension on the part of those engaged in plutonium work. This statement is not meant to belittle the absolute toxicity of plutonium in any manner. Animal experiments suggest that Pu^{239} deposited in bone is potentially more dangerous than Ra^{226}, and quite small amounts of radium have produced disabling and fatal bone disease in man.[1–4]

The physiological and toxicological properties of Pu^{239} are summarized in this report to provide better understanding of its potential as an industrial hazard and to explain further the necessity for rigorous industrial hygiene and engineering control over all plutonium processing.

RADIOACTIVE PROPERTIES OF PLUTONIUM-239

Plutonium^{239} decays by α-emission, emitting α-particles with an average energy of 5.15 MeV and having a range of about 40 μ in water and soft tissue. It emits several weak X-rays with

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energies of from 10 to 22 keV and a few 380 keV γ-rays. Material produced at high power levels emits fast neutrons ($\sim$1 MeV) from spontaneous fission of Pu^{240} and a negligible amount of 60 keV γ-radiation from Am^{240}. Heavily neutron-irradiated plutonium will, of course, give off β- and γ-radiation in relation to the quantity and age of the fission products present. The radiological half-life of Pu^{239} is 24,400 years. One microgram (1 μg) of this material is equivalent to 0.064 μc, or approximately 1.4×10^5 α-disintegrations per min.

PHYSIOLOGICAL PROPERTIES OF PLUTONIUM-239

Absorption

Gastrointestinal tract. Experiments on mature rats[5–9] and pigs[10,11] indicate that only from 0.01 to 0.003 per cent of an orally administered dose of Pu^{239} is absorbed into the blood stream. The extremely low gastrointestinal absorption rate appears to be essentially independent of the valence state of the plutonium and the amounts ingested[7,8] but somewhat dependent on the acidity of the plutonium solution.[8,12] That which is not absorbed is apparently hydrolyzed, adsorbed to the food residues, and passed out in the feces within 24 to 36 hr.

Intact skin. Absorption of Pu^{239} through the unbroken skin has been studied in man and in experimental animals. The percentage of applied plutonium absorbed through the skin of rats was shown to be independent of the area of skin exposed and the plutonium concentration but dependent upon the acidity of the plutonium solution applied.[13–15] Over a 5 day period, about 0.3 per cent of the plutonium applied in 0.1 N nitric acid was absorbed. When the nitric acid was increased to 10 N, the absorption was approximately 2 per cent. The skin of the rat, however, is quite different from human skin, especially from that of the palm of the hand (which is the area most likely to be contaminated). An experiment on man in which 10 μg of plutonium as $Pu(NO_3)_4$ in 0.4 N nitric acid was applied to the palm and allowed to remain for 8 hr gave an absorption rate of approximately 0.0002 per cent per hr.[16]

Wounds. Plutonium salts may be introduced into the body through abrasions, cuts and punctures in the skin. Microgram amounts of plutonium oxide placed on freshly abraded areas of the skin of rabbits failed to show any absorption into the body, but the oxide was incorporated into the scab and was lost when the scab became detached.[17] Pieces of plutonium metal (ranging in size from 0.67 to 1.8 mg) implanted subcutaneously in rabbits and rats were rapidly oxidized, but most of the oxide remained localized at the site of implantation.[18] Absorption into the body ranged from 0.09 to 1.2 per cent of the implanted dose over the entire life span of the animal (260 to 1048 days). Absorption of soluble plutonium salts through skin lacerations in rats has been reported as being greater than through the intact skin.[19] Scott and co-workers[20] showed that intramuscular injection of Pu^{3+}, Pu^{4+}, and PuO_2^{2+} resulted in absorption of 23, 4 and 30 per cent, respectively, from the site of injection after a period of 4 days, indicating a slow rate of plutonium translocation to other organs and tissues of the body. These experiments, as well as observations of actual accidents occurring in processing operations, show that introduction of plutonium and its compounds into wounds in the skin and subcutaneous tissues (especially in the case of cuts and puncture wounds) can result in significant but slow absorption into the systemic circulation.

Lungs. The problem of lung absorption, retention and elimination of inhaled materials is almost hopelessly complex, since the various factors are dependent on particle size of the material inhaled[21], solubility,[22] particle density,[23] rate of respiration of the individual,[24] etc. Although it is not possible at present to determine quantitatively what happens to inhaled plutonium under all specific conditions of exposure, it is possible on the basis of animal experiments to make some broad generalizations.[25]

If 100 radioactive particles of optimum size for lung retention are inhaled, about 25 are immediately exhaled without depositing in the lungs. Of the 75 particles that remain in the lungs 50 are deposited in the bronchial tree and removed in a few hours to a few days by ciliary action and swallowed. Of the remaining 25 particles which were deposited in the alveolar

Table 2. Distribution of Pu^{239} *in man following injection of* Pu^{4+} *complexed with citrate*

Tissue or organ	Weight of organ or tissue (g)	Plutonium per organ (%)*
Skeleton (including marrow)	10,000	66
Liver	1700	23
Spleen	300	0.4
Kidneys	700	0.4
Lungs	1000	1.0
Lymphoid tissue	700	0.5
Heart	300	0.1
Gastrointestinal tract	2000	0.5
Muscle and skin	36,100	3.9
Blood	5400	0.2
Balance	11,800	1.0
Excreted (urine and feces)	—	5.0
Total	70,000	102

* Expressed as percentage of injected dose.

in deposition patterns of radium and plutonium is believed to be the principal reason for the greater relative radiotoxicity of the latter.

Excretion and retention

Excretion of Pu^{239} has been studied in rats,[5] dogs,[30] pigs[31] and man.[25] Although species variations occur, the rate of excretion by all species is slow. The plutonium elimination rate of the dog is comparable to that of man, and unlike man and the dog, rats eliminate fifteen times as much plutonium in the feces as in the urine. Fig. 2 shows the urinary and urinary plus fecal excretion of plutonium by man (over a period of approximately 5 years) as a function of time after administration. Empirically, the urinary excretion curve (curve II) fits the following power function:

$$Y_u = 0.20 \times t^{-0.74}, \qquad t > 1 \qquad (1)$$

in which Y_u is the percentage of the administered dose excreted per day, and t is the number of days between exposure and collection of the sample. A recent resurvey of the early Los Alamos plutonium exposure cases suggests that this expression holds reasonably well over a period of at least 12 years. The fecal excretion curve (not shown in Fig. 2) is fitted by the expression:

$$Y_f = 0.63t^{-1.09}, \qquad t > 1 \qquad (2)$$

in which Y_f is the percentage of the dose excreted per day in the feces. The total urinary plus fecal excretion rate (Y_{u+f}) shown by curve I in Fig. 2 is represented by the sum of the two expressions. The corresponding expression for total urinary plus fecal excretion of Ra^{226} by man was given by Norris *et al.*[32] as:

$$Y_{u+f} = 28t^{-1.52}, \qquad t > 1. \qquad (3)$$

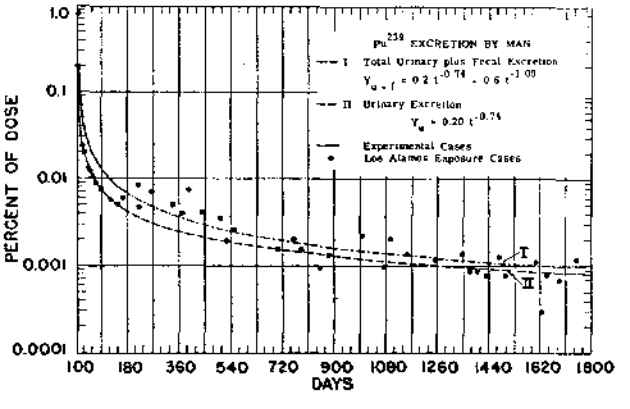

Fig. 2. Urinary and urinary plus fecal excretion of plutonium by man over a period of approximately 5 years.

good industrial hygiene practice. Wearing gloves while working with plutonium and routine hand monitoring twice daily are simple and effective control measures. Effective methods of skin decontamination are available. The standard Hanford procedure[33] of swabbing with liquid soap followed by a water rinse, and alternate $KMnO_4$ applications (4% solution) and $NaHSO_3$ (5% solution), is over 98 per cent effective. Versene (10% solution) is also very effective and less traumatizing to the skin.

Plutonium-239 embedded locally in the tissues. Plutonium introduced into the skin and subcutaneous tissues through lacerations and puncture wounds may remain at the site of the wound for a very long time. α-Radiation of the surrounding tissue, in this case, may produce local damage. Less than 1 μg of plutonium (0.064 μc) as $Pu(NO_3)_4$ injected subcutaneously into mice has reportedly resulted in formation of a malignant fibrosarcoma in the region of injection.[34] The probability of a fibrosarcoma being produced in man by subcutaneous introduction of similar amounts of plutonium is not known. Plutonium metal fragments (ranging in size from 0.67 to 1.8 mg), implanted subcutaneously into rabbits and rats,[19] did not produce fibrosarcoma. The metal was rapidly oxidized and the oxide progressively confined by the formation of collagenous connective tissue and calcification around the implantation site. From these studies, it may be concluded that plutonium metal and its oxides are relatively inert locally. One animal died, however, from an osteogenic sarcoma of the spine produced by skeletal deposition of plutonium absorbed from the implant.

The possibility of systemic absorption and local damage from plutonium embedded in the tissues necessitates industrial medical surveillance of potentially contaminated wounds. Over 50 per cent of particulate plutonium oxide contamination is removed from shallow abrasion-type wounds by normal surgical cleansing, and the rest is occluded in the scab and lost when the scab is detached. The extent of Pu^{239} contamination of lacerations and puncture wounds can be determined by external measurement of the 17 keV X-rays using a sodium iodide crystal spectrometer[35] and, at the discretion of the medical authorities, the contamination removed by surgical excision. Excision within a few days after injury can result in removal of most of the locally implanted plutonium.

Plutonium-239 in the gastrointestinal tract. Since the wall of the gastrointestinal tract has no cornified epithelium, Pu^{239} that is swallowed can produce α-irradiation of the mucosa during the 24–36 hr required to pass through the digestive system. Rats given 400 μg of Pu^{4+} in their drinking water for 5 consecutive days (total 2 mg) showed no signs of gross damage to the gut mucosa.[5] SULLIVAN and THOMPSON[36] administered Pu^{239} via stomach tube to approximately 200 g rats in doses of from 56 to 100 mc/kg of body weight (170 to 300 mg per animal) to see whether death could be produced and if so, whether the signs were similar to the intestinal radiation syndrome produced by irradiating the exteriorized gut with high doses of X-rays. The animals that received the lowest dose level showed no signs of damage. One out of four animals that received approximately 250 mg (88 mc/kg) of Pu^{239} died within 24 hr. Although the α-radiation dose to the intestine was estimated at about 650,000 rems, the mode of death showed no resemblance to the intestinal syndrome produced by large doses of X-rays. Lack of any signs of the acute radiation syndrome in the above experiments suggests little or no α-radiation of the radiosensitive basal cells of the gut mucosa, which in turn suggests little probability of radiation damage following chronic low level Pu^{239} ingestion.

Plutonium-239 in the lungs. The high incidence of lung cancer (predominantly bronchogenic carcinoma) among workers in mining operations in the Schneeberg and Joachimsthal districts of southeastern Europe was noted over 400 years ago.[37] Although the etiology of the miners' disease is still open to question, it is generally believed to have been associated with long inhalation exposure to the high concentrations of radon (3×10^{-6} μc/cm^3) and its daughters in the air of the mines.[38] LORENZ *et al.*[39] found a 50 per cent increase in pulmonary adenomas in mice after 9½ months of exposure to 8.8 r/day (total dose about 2400 r) of γ-radiation. Not only was the radiation dose relatively high and

comparable to those seen after an LD_{50}^{30} dose of whole body X-irradiation. The animals showed diarrhea, small areas of internal bleeding, loss of appetite, atrophy of the spleen, essentially complete destruction of the bone marrow and a disappearance of white blood cells.

Acute Pu^{239} toxicity studies in dogs showed essentially the same radiotoxicological signs and an LD_{50}^{30} of about 0.3 mg/kg. Beagle hounds given 0.27 μc/kg of Pu^{239} (equivalent to 300 μg in a 70 kg man) showed a drop in white blood cell count within 30 days, followed by a rapid return to a low normal count. A dose of 2.5 μc/kg produced an acute decrement in erythrocytes, leukocytes, heterophils and platelets with little tendency to return to normal.[42]

There is little doubt but that the signs of acute plutonium poisoning in man would be similar to those in the rat and the dog. Assuming man would respond to a weight basis like the dog or the rat, introduction of from 20 to 70 mg of Pu^{239} into the systemic circulation would result in a 50 per cent chance of death within 30 days. An individual surviving beyond 30 days would have an extremely poor prognosis and would surely succumb later to the chronic or delayed effects of such an overwhelming dose. The median survival time of rats that survived an acute LD_{50}^{30} was about 40 per cent of that of the controls. While the results of such a systemic exposure would surely be catastrophic, its probability of occurrence is extremely slight. With a gastrointestinal absorption rate of 0.003 per cent, an individual would have to ingest about $1\frac{1}{2}$ lb of plutonium. With a lung absorption rate of from 1 to 10 per cent, one would have to inhale from 0.2 to 2 g in the form of particles or droplets of a few microns or less in diameter. An explosive-type accident involving concentrated plutonium solutions and serious traumatic injury could conceivably occur in which lethal amounts of material could be deposited in the peritoneal cavity and absorbed.

Chronic or delayed effects. Animal experiments have shown beyond doubt that deposition in the skeleton of amounts of Pu^{239} too small to produce signs of acute damage may eventually produce serious bone pathology, including osteogenic sarcoma (Fig. 3). The latent period between exposure and appearance of damage is about 25 to 50 per cent of the normal life expectancy of the species. The induction period between time of exposure and time of appearance of tumors in eight cases of radium-induced malignancy in humans reported by Aub *et al.*[1] was 12 to 30 years, with an average of 23. These data and those reported by others[2–4] show that from 0.7 to 1 μc of Ra^{226} fixed in the skeleton for 25 years or longer may produce significant bone disease, and 0.8 μc has produced osteogenic sarcoma. Since information on the chronic or delayed radiotoxicity of Ra^{226} in man is available, the radiotoxicity of Pu^{239} is estimated from its tumorigenic potency relative to radium when administered to experimental animals.

Finkel[43] studied the relative potency of intravenously injected Ra^{226} and Pu^{239} for production of bone tumors in mice (Fig. 4).

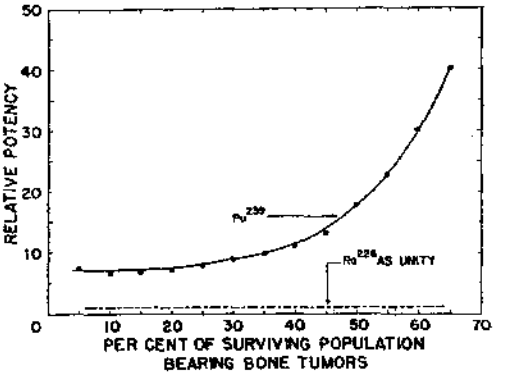

Fig. 4. Relative tumorigenic potency of Ra^{226} and Pu^{239} administered intravenously to mice.[43]

These data showed that plutonium was about thirty times as potent as radium when large enough doses were given to produce tumors in 60 per cent of the animal population. As the dose (and consequently the tumor incidence) decreased, plutonium showed a plateau in relative tumorigenic effect at about seven times that of radium. In these studies (using over 1400 mice), comparison was made on the basis of the dose injected. When the relative potency was compared on the basis of radiation dose to the skeleton (by allowing for relative skeletal retention of Pu^{239} and Ra^{226}, and the exhalation

are used to express U. The retained body burden (D_R) at time t following a single acute exposure is given by the expression:

$$D_R = 435Ut^{0.76}. \quad (5)$$

The exposure dose received by an individual as a result of chronic variable exposure of known duration (i.e. the time worked since the last negative urine assay) may be approximated from the assay of a 24 hr urine specimen and the same expression used for acute exposure occurring at known time (equation (4)). One may assume that the individual obtained all his body burden on the first day of exposure, in which case t becomes the elapsed time from beginning of work to the time of collection of the urine sample. Unless the individual actually did accumulate his body burden on the first day of work, such an estimate will be too high. One may assume also that the body burden was obtained on the last day of work, in which case t becomes the elapsed time between the last day of work and the time of collection of the urine specimen. In this case, the estimate may be too low. One may also average the results obtained on the basis of the two assumptions made above. The average result, of course, has the greatest chance of carrying the smallest error.

Following chronic invariant exposure to Pu^{239} (as might occur under conditions where air concentrations are rigidly controlled, the work highly routine, and the material uniformly distributed throughout the working environment), the total body exposure (T_D) may be calculated from the expression:

$$T_D = \frac{130 \times m \times U_n}{(n + \frac{1}{2})^{0.26} - (n - m + \frac{1}{2})^{0.26}} \quad (6)$$

where m is the duration of exposure (in days), n is the time from beginning of exposure until urine sample was taken, and U_n is the amount of Pu^{239} found in the 24 hr urine sample. Although the above expression is derived from the basic urinary excretion equation, it probably has little practical application to plutonium processing, where the materials are usually not distributed uniformly throughout the working environment.

Because of fluctuations in urinary excretion and statistical variations in the method of analysis, plutonium body burden (in actual practice) is not determined from a single urine sample but from a series of samples.

Several methods for determination of Pu^{239} in urine have been devised. The most sensitive procedure is the one developed by SCHWENDIMAN *et al.*[45] The urine sample is wet ashed with nitric acid and the plutonium coprecipitated with lanthanum fluoride. After further separation by extraction with thenoyltrifluoroacetone in benzene, the plutonium is converted to PuO_2^{2+} and electrodeposited on a stainless steel disk. The disk is placed in contact with a nuclear track α-plate for approximately 1 week, and the number of tracks registered on the developed plate are counted visually with a microscope. Plutonium recoveries of 85 ± 5 per cent are obtained routinely, and the detection limit at the 99 per cent confidence level is about 0.05 d/m per 24 hr urine sample (3.6×10^{-13} g of Pu^{239}). Although the above method is the one of choice for estimation of small plutonium body burdens, it is extremely tedious and time-consuming and several days are required to obtain a result. In an emergency involving potentially high exposure, a more rapid, less sensitive, method is highly desirable. A satisfactory procedure consists of digesting a 200 ml urine sample with HNO_3, followed by two lanthanum fluoride coprecipitations. The second precipitate is dissolved in aluminum nitrate solution and the plutonium extracted with thenoyltrifluoroacetone in benzene. The extract is evaporated in a counting dish and counted in a proportional α-counter.[46] The result can be obtained in about 2 hr after collection of the sample.

ACCELERATION OF PLUTONIUM-239 EXCRETION

Numerous attempts to remove Pu^{239} from the animal body have been made. Three substances that have shown promise are ethylenediaminetetra-acetic acid,[47] diethylenetriaminepentaacetic acid[48] and zirconium citrate.[49] The first two are strong complexing agents that mobilize plutonium into the blood stream and accelerate its excretion via the kidneys.

period, twenty-seven workers accumulated Pu^{239} body burdens of 0.1 μg or greater. Eleven accumulated levels equal to or greater than the presently accepted maximum permissible body burden, three of which were about twice that amount. Most of the exposures were believed to have occurred via inhalation as evidenced by the strong correlation with frequent contamination of the nasal vestibule determined by counting nasal swabs rotated in the nares immediately following highly contaminated operations.

The air-borne activity to which some of these persons were exposed was occasionally orders of magnitude above presently accepted maximum permissible air concentrations. On one occasion, the nasal swabs from an individual yielded over 1 μg of plutonium from each nostril. His body burden after this and several other similar operations was only 0.5 to 1 μg.

Twenty-four of the twenty-seven Los Alamos cases are being followed routinely at 3 year intervals for any signs of chronic or delayed effects. Complete general physical examinations, including laboratory tests, hematological studies, and X-rays, are conducted. Roentgenograms include pelvis, chest, skull, knee, elbow, hand and jaw. The roentgenograms are studied for signs attributable to plutonium. At the 9 year period, all observations were negative. When contacted in preparation for the 12 year follow-up examination, all subjects reported a continued state of normal health. Although the critical period for appearance of chronic effects has not passed, the complete negative character of the observations is encouraging.

DISCUSSION

Because of the superior fission properties of Pu^{239}, the future of the plutonium processing industry and the plutonium specialist is assured. However, because of the potential hazard of plutonium, assured also is the future of the industrial hygienist, the safety engineer and the industrial physician. What then is the situation with regard to the necessity for elaborate industrial engineering control of processes involving large amounts of this material? Management's prime consideration, of course, must be the health of the employee, since relatively small amounts of plutonium taken into the body and deposited in the skeleton may may predispose the individual to serious bone disease many years later. The maximum permissible body burden (0.04 μc) is considered safe in this respect. There are, however, important secondary factors that management must consider also. These may be illustrated by means of the following hypothetical example.

Suppose a young metallurgist, "John Doe", at the age of 21 accepts a position with a hypothetical company, "Plutonium Rocket Motors, Inc." Without adequate knowledge of the basic physiology and toxicology of plutonium, the first thing that is apt to happen to Mr. Doe (when he sees the elaborate industrial engineering control and persistent monitoring for air and surface contamination, is asked to wear protective clothing and rubber gloves, keep a respirator always at hand, check his hand contamination frequently, and submit routine urine samples) is an unwarranted fear for his personal health and safety. His apprehension could result in his creating a greater potential hazard to himself and those about him.

Let us assume also that in a few years Mr. Doe has become a highly skilled specialist in alloying, casting and welding plutonium metal, but in the process has accumulated a maximum permissible body burden. Although there is no reason to feel that his physical well-being has been jeopardized, he will still have 80 to 90 per cent of his body burden at retirement age and technically should be removed from further contact with plutonium for the remainder of his working lifetime. In this case, the company has lost the technical skill of an important specialist.

Furthermore, the question arises as to what the management can do with Mr. Doe. The problem of removing an employee from his job, in the interest of his health or well being, is not unique to the plutonium industry. Other industries have faced similar dilemmas. The alternatives are as follows: (1) The company can discharge Mr. Doe, which most certainly will do little to further labor–management relations. Moreover, Mr. Doe may choose to test the legality of the action. (2) Management can transfer Mr. Doe (the action taken usually by other industries) to other technical work not involving plutonium, or promote him to an

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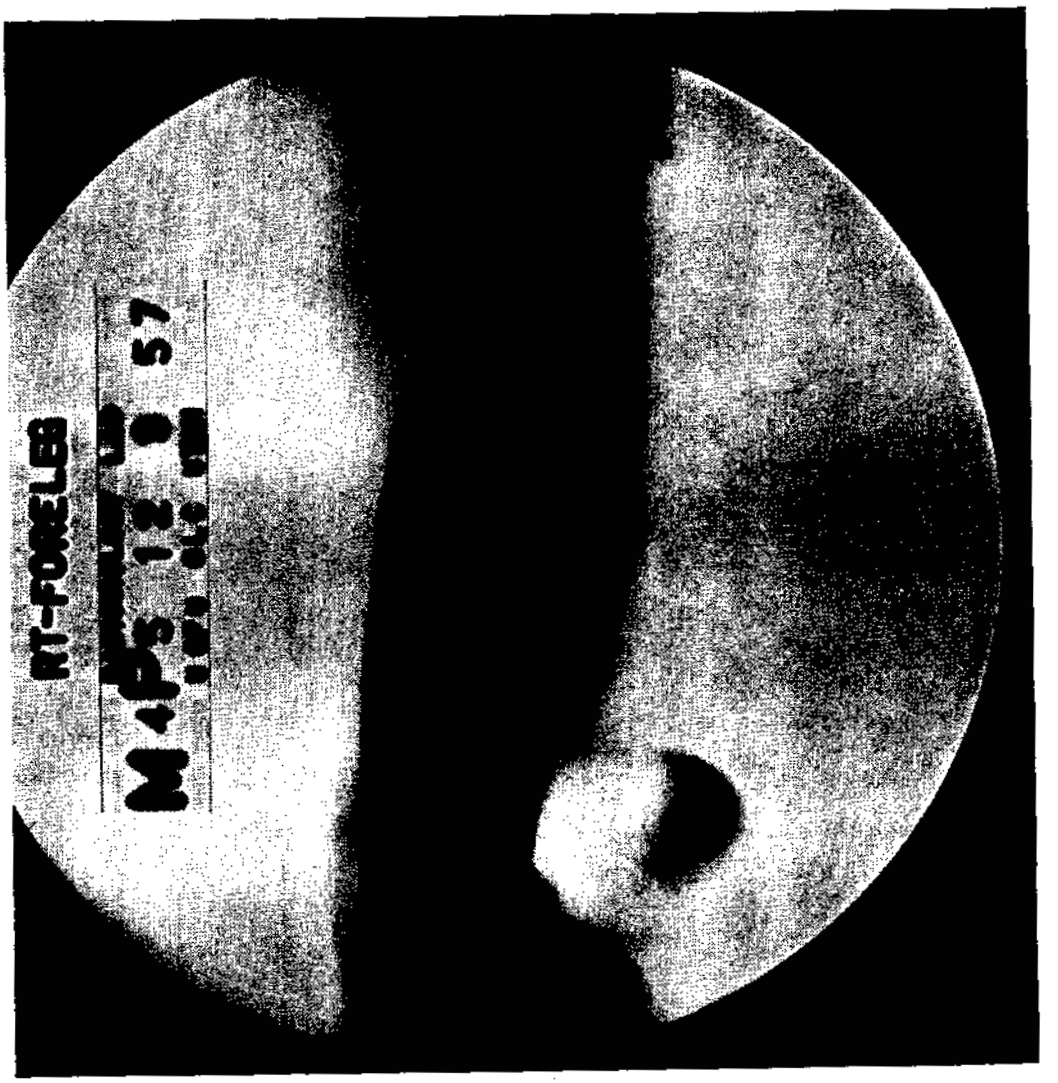

FIG. 3. Osteogenic sarcoma in a dog approximately 4 years after a retained dose of 2.5 μc Pu^{239} per kg body weight.

(Courtesy of W. R. Christensen and C. E. Rehfeld, Radiobiology Laboratory, University of Utah.)

FIG. 1. Autoradiograph showing plutonium deposition on the surface of a trabecula of the proximal humoral head in a dog sacrificed 24 hr after injection.
(*Courtesy of W. S. S. Jee, Radiobiology Laboratory, University of Utah.*)