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

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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.

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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

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

sacs, about 10 (10 per cent of the originally inhaled dose) are rather rapidly absorbed into the circulating blood and deposited predominantly in the skeleton. The remaining 15 particles may be phagocytized, deposited in the lymph nodes, or eliminated up the bronchial tree and swallowed, the time of removal being of the order of from 150 to 200 days. Experimental data on animals, at least in so far as plutonium oxide is concerned,[26] suggest that 10 per cent absorption may be a conservative upper limit. Absorption may actually be more nearly 1 per cent. Nevertheless, the data do suggest that inhalation is the principal potential route of entry of plutonium into the body. Experiments on animals show also that some of the inhaled material may accumulate in the pulmonary lymph nodes from which the elimination rate is slow, resulting several days later in a higher concentration in the nodes than in the lungs proper.[26,27]

Body deposition

Regardless of method of administration, plutonium is rapidly cleared from the blood stream and fixed in the tissues. Table 1 shows the rate of disappearance of Pu^{239} from the blood of man following intravenous administration of a small dose of Pu^{4+}-citrate. Approximately 65 per cent of the plutonium was removed from the blood in 4 hr, and about 85 per cent was removed in only 1 day. Plutonium in the blood is believed to be combined largely with the globulin fraction of the serum proteins, and regardless of the valence of the material administered it is believed to be all in the form of Pu^{4+} within a few hours.

Although the relative distribution of plutonium in the various tissues and organs is somewhat dependent on chemical form and method of administration, liver and skeleton are the major sites of deposition. When administered as a strong complex (e.g. citrate or versenate) or as PuO_2^{2+}, from 60 to 80 per cent of the dose is deposited in the skeleton and from 10 to 20 per cent in the liver. When injected as uncomplexed Pu^{3+} and Pu^{4+}, liver deposition is approximately 25 and 40 per cent and skeletal deposition approximately 45 and 30 per cent, respectively.[5] The greater liver uptake following intravenous injection of uncomplexed Pu^{3+} and Pu^{4+} may be explained by complex colloid formation at the pH of the blood, resulting in greater reticuloendothelial fixation.

Table 1. Plutonium-239 content of total blood volume as a function of time after administration*

Time after administration	Pu^{239} in blood (%)†
4 hours	36
1 day	16
2 days	10
3 days	8.6
6 days	3.4
10 days	1.2
15 days	0.7
22 days	0.4

* Total blood volume taken as 7.7 per cent of body weight.

† Percentage of administered dose.

Distribution of Pu^{239} in man about 5 months after injection of Pu^{239} complexed with citrate is shown in Table 2. About 90 per cent of the injected material was deposited in only two organs (67 per cent in the skeleton and 23 per cent in the liver). Slower entry of plutonium into the blood stream (e.g. via absorption from the gastrointestinal tract and the lungs) as opposed to intravenous injection may give greater deposition in the bone and less in the liver.[5] A few months after systemic exposure to plutonium, from 80 to 90 per cent of the total body burden may be found in the skeleton, where it is believed to be adsorbed on the surfaces of newly formed and rapidly metabolizing bone mineral.[28]

Autoradiographs of bone sections (Fig. 1) show the material deposited in a fine line paralleling the endosteal and periosteal surfaces with highly localized concentrations in regions of trabecular bone.[29] The deposition patterns of plutonium and radium, although grossly similar, are somewhat different microscopically. Because of its similarity to calcium, radium is chemically incorporated into bone mineral, giving a more diffuse deposition pattern with time than does plutonium. This basic difference

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.)

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:

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

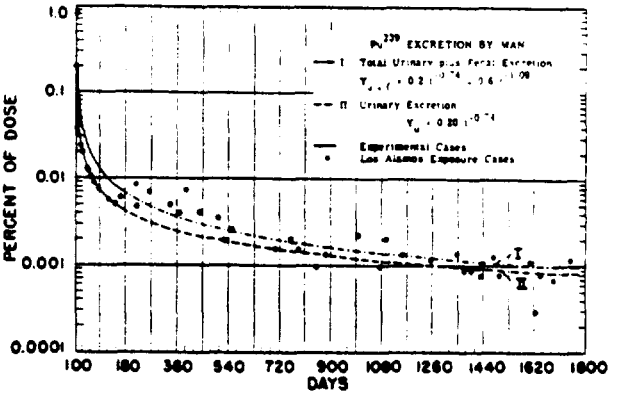

Fig. 2. Urinary and urinary plus fecal excretion of plutonium by man over a period of approximately 5 years.

A number of factors regarding the excretion and retention of plutonium by man are apparent from the above expressions. First, the plutonium excretion rate is not a simple exponential but becomes slower as the period of fixation becomes longer. That is to say, the elimination half-time increases with time. Second, the fecal to urinary excretion ratio is not constant. During the first 30 days, the ratio is slightly greater than 1, after which it drops to less than 1, becoming progressively smaller with time. Third, the excretion rate of plutonium is extremely low; less than 1 per cent is excreted during the first 24 hr after administration, compared to from 30 to 40 per cent for Ra^{226}. The rate of Pu^{239} excretion continues to decrease with time until only about 0.01 per cent is being excreted per day at about 100 days after exposure. At approximately 5 years, the rate has dropped to about 0.001 per cent. Table 3 shows the relative accumulated excretion of plutonium and radium at various times after exposure. These data were obtained by integrating the respective excretion expressions between the limits of 1 and t days after exposure. These data show that an individual may be expected to retain about 80 per cent of his original plutonium body burden 50 years after exposure, while he would be expected to retain only about 0.3 per cent of his original body burden of radium. Solution of the integral expression for 50 per cent excretion shows that approximately 200 years would be required for man to eliminate half his plutonium body burden.

Table 3. Accumulated urinary plus fecal excretion of Ra^{226} and Pu^{239} by man

Time after administration	Accumulated excretion (% administered dose)	
	Ra^{226}	Pu^{239}
1 day	46	0.5
10 days	84	2.6
50 days	93	4.0
100 days	95	4.7
1 year	97.5	6.3
3 years	98.6	7.8
5 years	98.9	8.7
10 years	99.2	10.0
20 years	99.5	12.2
50 years	99.7	17.6

RADIOTOXICOLOGY AND INDUSTRIAL MEDICAL CONTROL OF PLUTONIUM-239

The maximum permissible body burden of natural uranium, based on chemical toxicity to the kidney, is about 40 mg. Plutonium is chemically very similar to uranium and may be expected to have about the same chemical toxicity. Because of its greater specific activity (about 2×10^5 that of uranium), it may be considered entirely as a potential radiological hazard.

External radiation from plutonium-239. Plutonium-239 presents no potential external α-radiation hazard when deposited on the skin, since the α-particle range in tissue is about 40 μ and the cornified (dead) epithelium of the skin surface is from 70 to 150 μ thick. Plutonium-239 does, however, emit weak X-rays with an average energy of about 17 keV and some neutrons (~1 MeV energy), depending on the Pu^{240} content. The X-ray emission is much too soft to produce a general external hazard; however, the radiation dose rate to the skin of the hands, when in contact with unclad Pu^{239} metal, is about 1 rad/hr. Through heavy neoprene drybox gloves, the dose rate is about 400 mrads/hr, giving a maximum permissible weekly contact time of about 4 hr. Under usual conditions, the external radiation hazard from neutron emission is considered negligible. Plutonium that has been irradiated with neutrons will, of course, contain fission products which will present a β–γ radiation hazard that will be dependent on the quantity and age of the fission products present.

Plutonium-239 contamination of the skin. As mentioned above, there is no potential external alpha radiation hazard associated with Pu^{239} deposited on the intact skin surface. The possibility of a small but finite absorption rate of plutonium through the skin and from contaminated wounds and the possibility of transfer of activity from the hands to food, cigarettes, etc., make control of hand contamination a

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

the incidence of pulmonary tumors relatively low, but lung adenoma is very common in many mouse strains and has little resemblance to the tumors seen in the Schneeberg and Joachimsthal miners.

TEMPLE *et al.*[40] reported the effect of intratracheally injected $Pu^{239}O_2$ using "pluronics" as a suspending agent on the incidence of benign pulmonary papillary cystadenoma in BAF_1 mice. They found 33 per cent of the animals that received only 0.0033 μc of Pu^{239} developed lung tumors. The spontaneous incidence of papillary cystadenoma in untreated BAF_1 mice, however, was 17 per cent: the incidence in animals treated with the suspending agent only, with nonradioactive ruthenium oxide, and with 1225 r of whole body X-irradiation was 19, 28 and 62 per cent, respectively. While such observations give interesting relative information, they may not provide quantitative data on the absolute carcinogenicity of Pu^{239} particulates in the lung. These same authors, however, did find two malignant squamous cell carcinomas in BAF_1 mice 400 days after intratracheal injection of 0.006 μc of plutonium as $Pu^{239}O_2$ and one fibrosarcoma 500 days after administration of only 0.003 μc.

Production of bronchogenic cancer and other changes in the lungs of rats by β-radiation have been demonstrated with large doses 3.2 to 200 μc per animal of Ce^{144} introduced into the lungs by tracheal intubation.[27] Introduction of lung tumors in experimental animals by other radioactive materials Po^{210}, $BaS^{35}O_4$, Ru^{106}-oxide and Sr^{90} have been observed also.[27] In almost all cases, the estimated radiation doses to the lungs were about 2000 rads or greater. These observations show that lung cancer can be produced by ionizing radiations and that the lungs are only moderately radiosensitive.

Plutonium deposited on the lung parenchyma in insoluble form may eventually find its way into the lymph nodes, where it may remain indefinitely.[25,26] Under conditions of long-term chronic inhalation exposure, it is possible that the pulmonary nodes may receive a greater α-radiation dose than the bone. Although there has been little observation of specific malignancy associated with lymph node accumulation of radioactive material, its potential hazard cannot be evaluated at present. The possibility of lymph node accumulation and the question of radiosensitivity of lymphoid tissue certainly suggest the need for more research on this particular aspect of plutonium radiotoxicology.

The relatively high rate of plutonium absorption from the lung from 1 to 10 per cent of the amount inhaled, its low maximum permissible systemic burden (0.04 μc), and its 200 year biological half-time necessitate rigorous control of air concentrations in the working environment. If the lung absorption rate is indeed from 1 to 10 per cent, then the lifetime exposure of the respiratory system can be only from 0.4 to 4.0 μc. This rather strenuous limitation on lifetime inhalation exposure affords considerable protection against the potential risk of lung disease from plutonium processing.

The rigorous control of plutonium air concentrations in the working environment is largely responsible for the expensive and elaborate closed-system processing techniques that are now standard throughout the plutonium processing industry.

Skeletal deposition

Once in the blood stream, Pu^{239} is rapidly deposited in the tissues, predominantly in the bone and the liver.[5] The skeletal system is usually considered the critical organ, since it accumulates the majority of the activity and retains it essentially throughout the lifetime of the individual. Large amounts of Pu^{239} deposited in the bone and liver can produce acute or immediate radiotoxicological effects. Much smaller amounts may result many years later in bone cancer, chronic anemia, osteoporosis and bone necrosis (which may result in spontaneous bone fractures), and other symptoms seen in cases of chronic radium poisoning.

Acute effects. Relatively large amounts of Pu^{239} (500 μg/kg body weight) injected intravenously into rats produced an anemia that lasted about 90 days and an abnormally low white blood cell count that persisted throughout life.[41] Doses of 1 mg/kg body weight produced death in 50 per cent of the animals within 30 days after injection. In most cases, death occurred in from 9 to 14 days with signs

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.)

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 1½ 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).

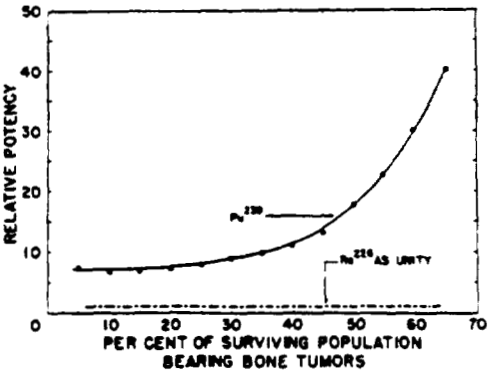

Fig. 4. Relative tumorigenic potency of Ra^{226} and Pu^{239} administered intravenously to mice.[43]

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

of radon by the mouse), Pu^{239} was about four times as tumorigenic as Ra^{226}.

About 8 years ago, the AEC established a project at the University of Utah to study the relative radiotoxicity of Ra^{226}, Pu^{239}, MsTh Ra^{228} and RdTh Th^{228} in mature beagle hounds. The injected doses of the various nuclides were such that the amounts (in μc/kg body weight) retained by the animals were equivalent to from 10 to 1600 times the presently accepted maximum permissible body burden (0.0014 μc/kg) of Ra^{226} for man. Some of these animals have carried their body burdens for about 6 years, and extensive bone pathology (including bone tumors) has occurred in the high dosage groups.[44] Four animals that retained the Pu^{239} equivalent of 180 times the human maximum permissible Ra^{226} level have died of bone tumors. No tumors have yet developed in the dosage group that is sixty times the human maximum permissible level. These observations cannot be used at present as an indication of the absolute Pu^{239} tumorigenic dose, since the experiment still has several years to go and tumors may occur yet in the lower dosage levels. The data at the present time do indicate, however, that Pu^{239} indeed may be about five times as hazardous (on the basis of equivalent radiation dose to the skeleton) as Ra^{226}.

The obvious industrial medical regulation of the potential hazards of internally-deposited Pu^{219} is to control all its potential routes of entry into the systemic circulation such that the probability of workers accumulating appreciable body burdens is small.

MAXIMUM PERMISSIBLE BODY BURDEN OF PLUTONIUM-239

The use of Ra^{226} (and MsTh) in the luminous dial industry, public consumption of radium-rich waters, and the therapeutic application of radium by the medical profession have provided information on the radiotoxicology of this material in man. On the basis of these experiences, the National and International Commissions on Radiological Protection adopted 0.1 μc as the maximum permissible burden of Ra^{226} for occupational exposure. The maximum permissible body burden may be defined as the maximum amount of material that can be maintained indefinitely in the adult human body without producing significant bodily injury to any person at any time during his natural lifetime.

Since Pu^{239} (like radium) emits most of its radiant energy as α-particles and concentrates predominantly in bone, the skeleton is considered the critical organ and the maximum permissible body burden for occupational exposure is determined by comparison with that of Ra^{226}. The maximum permissible body burden q may be estimated by the following expression:

$$q = \frac{q_{Ra} \times f_{Ra} \times E_{Ra}}{f_{Pu} \times E_{Pu} \times 5} = \frac{0.1 \times 1 \times 10.4}{0.9 \times 5.3 \times 5} = 0.043\ \mu c$$

in which q_{Ra} is the maximum permissible body burden of Ra^{226}, f_{Ra} and f_{Pu} are the respective fractions of total body radium and plutonium deposited in the skeleton, E_{Ra} is the energy (in MeV) deposited in tissue per Ra^{226} disintegration (taking into consideration recoil energy, daughter decays and fractional loss of radon by exhalation), E_{Pu} is the energy per Pu^{239} disintegration (including recoil energy), and 5 is the radiotoxicological potency of Pu^{239} relative to Ra^{226} as determined by animal experiments. On this basis, 0.04 μc is the maximum amount of Pu^{239} which, when fixed indefinitely in the human body, has the same improbability of producing significant bodily injury as does 0.1 μc of Ra^{226}.

ESTIMATION OF PLUTONIUM-239 BODY BURDEN

An individual's Pu^{239} body burden may be determined from a 24 hr urine analysis[25] and the urinary excretion expression given as equation (1). Following a single acute exposure occurring at known time, the body burden (D_E) at time of exposure is given by the expression:

$$D_E = 500 U t^{0.74} \qquad (4)$$

where U is the amount of Pu^{239} found in a 24 hr urine sample collected t days after exposure. The body burden at time of exposure is given in whatever units (c/m, d/m, μc or μg)

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.

Zirconium citrate is believed to exert its effect through a colloidal ion exchange process in which the final disposition of plutonium follows that of the zirconium colloid. All three treatments are most effective if applied immediately after exposure before the plutonium has become fixed in the bone. Diethylenetriaminepenta-acetic acid looks promising in animal experiments but has not been tried in humans. Rats treated 1 hr after intravenous Pu^{239} injection showed 9 per cent fixation of plutonium in the skeleton, compared to 61 per cent for untreated controls. Animals treated several times per week for 4 weeks, beginning 38 days after plutonium injection, had about half the skeletal burden of untreated controls.[48] Rats treated with zirconium citrate at 1 hr after plutonium injection showed 20 per cent deposition in the skeleton, compared to 68 per cent in untreated controls.[49] Treatment of human exposure cases, however, has met with little success.[50]

FOREMAN *et al.*[51] reported treatment of two Pu^{239} exposure cases with ethylenediaminetetra-acetate. In one case, treatment was begun 5 days after exposure and produced a decrease of about 25 per cent in the individual's body burden. Better results might have been obtained had treatment been started earlier. Treatment of the second individual, who had accumulated plutonium through long continued chronic exposure, failed to produce a significant change in the body burden. Ethylenediaminetetra-acetic acid has been shown to produce kidney damage.[52] Since kidney damage from ethylenediaminetetra-acetate is believed to be related to its strong complexing action for divalent ions, diethylenetriaminepenta-acetate may be nephrotoxic also.

The decision to treat or not to treat a case of plutonium exposure is difficult. Each case must be decided individually and, since the methods of treatment become less effective with time, the decision should be made as soon as possible. One microcurie of Ra^{226} (ten times the maximum permissible body burden) has produced serious bone disease in a few individuals. Ten times the maximum permissible body burden of Pu^{239} (0.4 μc) might be expected to produce severe bone changes in a few individuals also. The treatment of cases with several times the maximum permissible body burden would certainly seem justified. Indiscriminate treatment, however, should be avoided in view of the potential toxicity of the drugs.

HUMAN EXPERIENCE WITH PLUTONIUM-239 EXPOSURE

Occupational exposures to Pu^{239} have occurred at the Los Alamos Scientific Laboratory, General Electric's Hanford Atomic Products Operation (Richland, Washington), Canadian Atomic Energy Agency (Chalk River), and the British Atomic Authority.

PARKER[53] reported the plutonium exposure history of 10 years of operation of the General Electric's Hanford facilities. One hundred cases of positive plutonium exposure have been detected. There has not been a single case of overexposure, and in only two cases was the body burden greater than 50 per cent of the maximum permissible level. In 70 per cent of the cases, the exposures were 10 per cent or less of the maximum permissible body burden. Fifty-five per cent of the cases were associated with known exposure incidents and 45 per cent with chronic exposure under apparently normal working conditions. Of the cases associated with known exposure incidents, 75 per cent were exposed via inhalation. This supports the view long held at Los Alamos that absorption through the lungs is the major potential route of entry of plutonium into the systemic circulation.

The Canadian Atomic Energy Establishment at Chalk River had an accident in 1950 in which two individuals received plutonium exposure. One individual received a body burden of 0.15 μg (0.01 μc) and the other 0.10μg (0.006 μc). CIPRIANI[54] reported also that thirty-one out of 321 Chalk River employees tested during 1953–1954 had detectable Pu^{239} body burdens. The British Atomic Energy Authority had a contaminated accident at Harwell in 1952 in which a waste disposal worker received a body burden of approximately 5 μg (0.32 μc). The mode of exposure was not known, but it was probably via inhalation.

The oldest exposure cases on record are those reported by the Los Alamos Scientific Laboratory.[55] Most of these occurred from the fall of 1944 through 1945. During this

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

administrative or supervisory position outside the processing area. In this case, there is the possibility that a a satisfactory job, involving no potential plutonium exposure, may not be available, or b Mr. Doe may not be qualified or may not wish to be an administrator or a supervisor. 3 The company can seek a settlement with Mr. Doe through its own devices or through workers' compensation laws, few if any of which specifically cover the particular type of claim.

Because of conscientious industrial medical and engineering control over all plutonium operations, management has rarely faced the situation of Mr. John Doe. The cases of maximum permissible exposure that occurred at the Los Alamos Scientific Laboratory occurred during and immediately after the War and were mostly young college graduates assigned to the Laboratory through the Manhattan District. Upon discharge, some returned to jobs unassociated with atomic energy development. Others remained at the Laboratory where, by virtue of their technical knowledge and ability, they progressed naturally to key administrative and supervisory positions. This fortunate circumstance, however, should not be expected to occur always.

In addition to continued rigorous industrial hygiene and engineering control of all plutonium operations, there are a few courses of action which seem to merit industry's future consideration. First, existing workers' compensation laws may be modified and new ones written to deal specifically with the industrial risks of the nuclear energy development program. Second, company insurance plans may be developed that protect both employee and employer in the event of a lifetime maximum permissible exposure. Third, the lifetime maximum permissible Pu^{239} exposure may be prorated against the employee's potential employment expectancy as is now customary for lifetime exposure to whole body irradiation. In this case, an employee's maximum permissible body burden should be:

$$\frac{0.043}{47}(N - 18) = 0.001(N - 18)\ \mu c$$

in which 18 is the legal employment age, 47 is the number of years of expected employment before retirement at age 65, and N is the chronologic age of the individual. There are a number of interesting facets to this proposal. 1 An individual's maximum permissible body burden is dependent only on his chronologic age and not on his length of employment. 2 Other things being equal, older people are favored as routine plutonium process operators. 3 An additional safety factor is provided in that an individual is not allowed his lifetime maximum permissible body burden until retirement age. 4 It is somewhat conservative in that it assumes an individual, once he is employed, will work with plutonium for the rest of his occupational lifetime.

Insistence on rigorous industrial engineering control does not mean that accumulation of a Pu^{239} maximum permissible body burden has any great probability of producing significant bodily injury. It means primarily that plutonium processing without such control would be contrary to good industrial hygiene and to the elementary principles of industrial management. If presently recommended industrial medical practices are maintained, there is little reason to feel that the health of an individual working with plutonium will be subject to any greater absolute risk than if he were driving a truck, operating a lathe, or working in an ordinary chemistry laboratory.

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