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Behavior of Plutonium in Animals and Man

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Most of this material is not my own work but that of many people, and if I miss giving the credits at the times they are required, I hope you will excuse me.

PLUTONIUM CHEMISTRY AND BIOLOGICAL BEHAVIOR

I hope you all remember what we heard this morning about plutonium chemistry, but, in case you do not, what follows is a brief review of the chemical properties of plutonium that are important to biology. These are the valence state, hydrolysis, insolubility of compounds, and formation of complexes. This morning you heard about the multiplicity of plutonium valence states. The Pu(III), Pu(IV), and Pu(VI) states are important biologically.

In biological experiments the quantities of plutonium involved are usually so small and the solutions are so dilute that, although disproportionation (the simultaneous presence of more than one valence state) does occur, the tendency to disproportionate is not so great as it is in more concentrated solutions.

Plutonium(IV) has been studied most in biology because it is the most stable under the kinds of conditions one encounters in biological systems. As long ago as the early 1940s, Scott et al. (1944) showed that the three plutonium valence states behaved quite similarly after administration to rats. They concluded that Pu(III) and Pu(VI) were not stable in biological systems with respect to Pu(IV) and that, regardless of the form administered, most of the plutonium would eventually end up as Pu(IV). From what we heard this morning, that may not be a correct interpretation, but it may also be that, even if Pu(III) and Pu(VI) are stable in biological systems, their behaviors are sufficiently like Pu(IV) that small differences are obscured by the ordinary variability of biological systems.

For the most part we will be discussing Pu(IV), at least as a starting material. Unless otherwise specified, "plutonium" should be understood to be Pu(IV).

Most plutonium compounds (like the compounds of other multivalent cations, such as the rare earths, the trivalent actinides, and iron) are sparingly soluble except in acid solution. Plutonium dioxide is one of the most insoluble of known compounds.

Highly positively charged ions of small size, such as Pu(IV), compete with hydrogen ions for hydroxyl ions in water in the reactions that were discussed this morning. For comparison, the first hydrolysis constant of Pu(IV) is 1.6; of Fe(III), 2.5; of Pu(III), 7; and of Ce(III), 9.6. Thus the tendency of Pu(IV) to hydrolyze is about like that of iron and is considerably greater than that of Pu(III) or cerium. In neutral or slightly alkaline solutions, Pu(IV) ions do not exist, and, in a solution of pH 8, uncomplexed plutonium is present only as the hydroxide. In dilute solutions the hydroxide exists as a colloid; in more concentrated solutions, as a polymer or a visible precipitate.

Highly charged ions of small size also form stable complexes with such entities as citrate and the aminopolycarboxylic acids, EDTA and DTPA. These agents also form stable complexes with the rare earths, the trivalent actinides, and iron. The multivalent cations also form complexes of variable stability with proteins in blood, liver, and bone.

Although all of the biological data have been obtained using pure plutonium compounds and nearly pure pluto-

nium isotopes, we must be aware that in modern reactor and fuel-processing technology the plutonium is not likely to be pure, either chemically or isotopically. Most of the biological studies have used ^{239}Pu. However, there appear to be some subtle effects on solubility and mobility, when the specific alpha activity is increased by approximately 280, as in the case of pure ^{238}Pu. Reactor plutonium is mixed, and its specific activity, although probably not so great as that of pure ^{238}Pu, is certainly going to be considerably higher than that of pure ^{239}Pu.

In addition, fuels will be largely uranium by weight. At the processing level the mixture also includes fission products and trivalent actinide by-products. In the event of an accident, the mixtures will also include the elements of the core assembly, the coolant, the containers, and mineral dusts.

BIOLOGICAL STUDIES

The plutonium compounds that have been studied biologically span the range of likely solubilities from the highly soluble Pu(VI) citrate to highly insoluble, high-temperature-fired PuO_2 ceramics. The routes by which plutonium compounds have been administered are shown in Fig. 1. They have been introduced into the lung, either by inhalation or by instillation of solutions; administered by mouth; placed in the soft-tissue compartment by injection under the skin or into muscle or into the peritoneal cavity; and introduced directly into the plasma compartment by intravenous or intra-arterial injection. Plutonium compounds have also been applied to intact or damaged skin. (Note: the incisor tooth compartment applies only to rodents, and transfer from the trabecular to the cortical bone compartment takes place so far as we know only during rapid growth.)

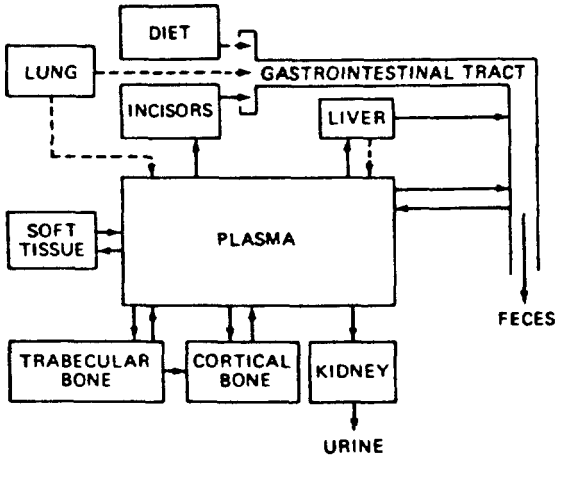


Fig. 1 Kinetic model of the metabolism of actinide elements in mammals. The incisor tooth compartment is present only in rodents. Reproduced from Durbin et al. (1967) with the permission of the publisher.

Although it seems unlikely that plutonium complexed with citrate will be encountered in real life, such soluble materials have been studied in order to examine the behavior of plutonium, separately from the problem of its transport across cell barriers. It is also unlikely in real life that insoluble plutonium particulates will be introduced directly into the plasma compartment, but studies have also been conducted of injected colloidal or polymeric plutonium in order to examine the errors of earlier experiments in which supposedly soluble plutonium was administered partly in colloidal form.

Insoluble plutonium compounds introduced into the gastrointestinal tract or the lung or into wounds are essentially local radiation sources. Impaired pulmonary function and lung tumors have resulted from deposition of plutonium compounds in the lung. Local tissue reactions result from plutonium deposits in wounds or beneath the skin. Daily feeding of plutonium to rats results in radiation damage to the intestine, and the severity is proportional to the dose. Apart from lung tumors, the amounts of plutonium required to produce these reactions are large, and the time for the development is long.

We know almost nothing, even now, about the exact mechanisms by which small amounts of plutonium, initially administered as insoluble compounds, are solubilized or otherwise transported into the body interior from their initial sites, chiefly the lung, the gastrointestinal tract, and wounds. In the case of the lung and intestine, the plutonium must be either rendered soluble so that it can participate in some process that will transport it across cell membranes or it must be trapped by cells that eventually carry or extrude their particulate contents into the body.

That particulate plutonium can be transported to some extent is shown by the transfer of inhaled $^{239}PuO_2$ from the lung into the pulmonary lymph nodes and from subcutaneous implants to local lymph nodes.

Insoluble plutonium introduced directly into the circulation by intravenous injection behaves in a way that is typical not of plutonium specifically but of colloidal material in general. Depending upon their size, colloidal particles are deposited in liver, spleen, and bone marrow. If the particles are large enough, they also are trapped in the lung capillaries.

Microscopic examination of these tissues reveals that they contain reticuloendothelial cells that trap and hold particulate matter. Autoradiographs reveal that colloidal plutonium is inside these specialized cells.

In cases of environmental or industrial contamination, it is not likely that particulate material will enter the circulation directly. Therefore, even though the literature on the distribution and behavior of colloidal plutonium is vast, we will move on to examine the deposition of plutonium which is soluble and which is distributed in the body by virtue of its chemistry rather than its physical state.

However, an understanding of the behavior of particulate plutonium trapped by phagocytes is important to understanding what happens to plutonium after it is deposited. Once soluble plutonium is deposited, it may be recirculated and redistributed within the animal; reticuloendothelial cells are frequently involved in that redistribution.

PLUTONIUM TRANSPORT IN BLOOD

Thanks to modern protein-chemistry techniques, we now know something about the way in which soluble plutonium is transported in the blood. There is a growing body of evidence that points to iron-transport mechanisms and iron-storage mechanisms as the underlying physiological processes that determine the fate of soluble plutonium.

One of the earliest observations of plutonium behavior was that intravenously injected soluble Pu(IV) or Pu(VI) remained in the circulation for many hours (Fig. 2), unlike strontium or the trivalent lanthanides which were cleared from the blood very quickly. In the case of strontium and the trivalent lanthanide or actinide elements, there is less than 0.1% circulating at 1 day. The solid symbols are from three people who were injected in 1945–1946. The HP-2 dashed line is approximately typical of the group of human cases. The squares are data from one individual in whom the plutonium residence time in the blood was particularly long.

The people were all middle-aged or older, and we compare them in Fig. 2 to healthy young animals—the young adult Beagle dog and a lactating Suffolk sheep (in the first or second pregnancy).

Muntz and Guzman-Barron (1947) interpreted the prolonged residence of the plutonium in blood as proof

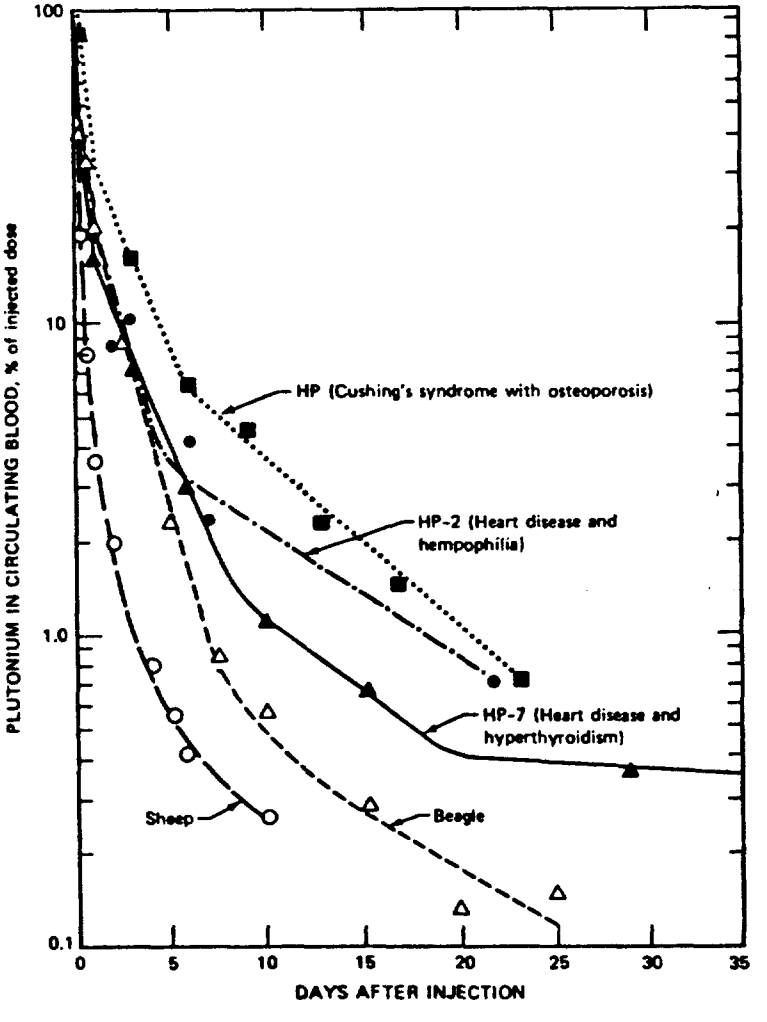


Fig. 2 Plutonium in the circulation after intravenous injection into human subjects, Beagle dogs, or Suffolk ewes. Reproduced from Durbin (1972) with the permission of the publisher.

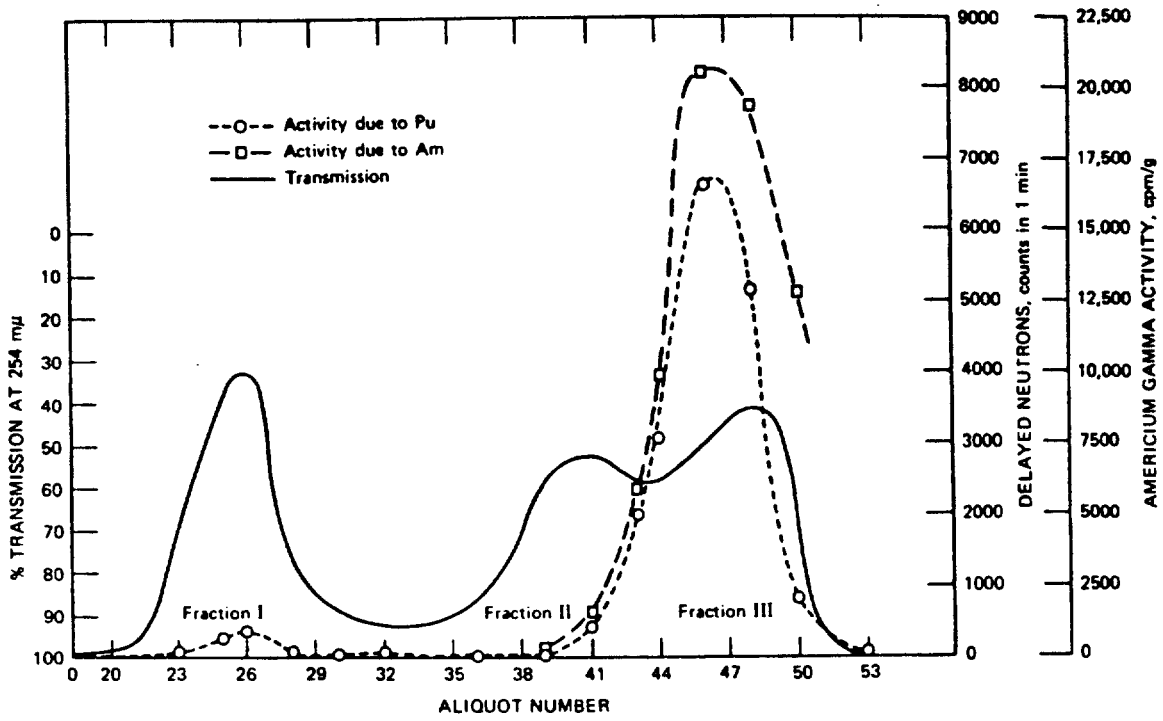


Fig. 3 Demonstration of the association of Pu(IV) and Am(III) with serum proteins of small size. Column is 93 by 2.5 cm. Buffer is 0.1M TRIS-HCl in 1M NaCl, pH 8.0. Temperature is 7 to 8°C. Flow rate is 8 to 9.5 ml/hr. Dialyzed serum sample applied is ~6 mL Reproduced from Popplewell and Boocock (1967) with the permission of the authors and publisher.

that plutonium was bound to a large molecule. They used an electrophoretic technique to demonstrate that plutonium was associated with a β_1-globulin in serum.

It was not until about 20 years later that Popplewell and Boocock (1967) in England applied modern protein-separation methods to this problem and identified the β_1-globulin as transferrin, the specialized protein that normally carries iron in mammalian blood. Figure 3 is taken from a paper they presented at a Hanford symposium in 1967. Serum proteins were fractionated by size; the larger globulins lie to the left; the smaller albumins to the right. The plutonium and also ^{241}Am are associated with the proteins of smaller size.

The protein peak containing the smaller proteins was separated by an ion-exchange technique into its two major components, "A" on the right, albumin; and "T" on the left, transferrin (Fig. 4). All of the plutonium is associated with the transferrin fraction.

Popplewell and Boocock (1967) further found that, when sodium citrate was added to the solution, the plutonium was separated from the transferrin (Figs. 5 and 6). They concluded that in the presence of excess of citrate ion the plutonium–transferrin combination was not stable.

Next they examined whether or not plutonium competed with iron for transferrin binding sites (Fig. 7; compare with Fig. 3). This is a size separation as in Fig. 3,

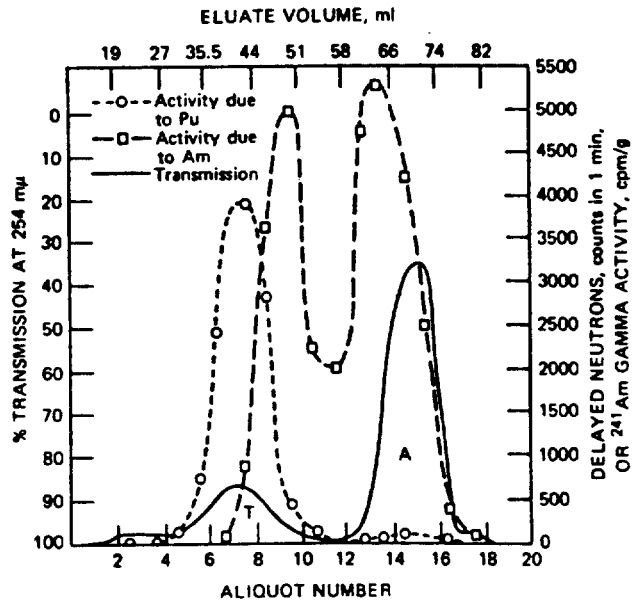


Fig. 4 Demonstration of the association of Pu(IV) with the transferrin fraction of serum proteins. Column is 28 by 1.6 cm. Buffer is 0.1M TRIS-HCl with gradient of 0.1 to 2M NaCl, pH 8.0. Temperature is 7 to 8°C. Flow rate is ~11.7 ml/hr. Volume fraction is ~4 mL Sample volume applied is 3.6 mL T = transferrin. A = albumin. Reproduced from Popplewell and Boocock (1967) with the permission of the authors and publisher.

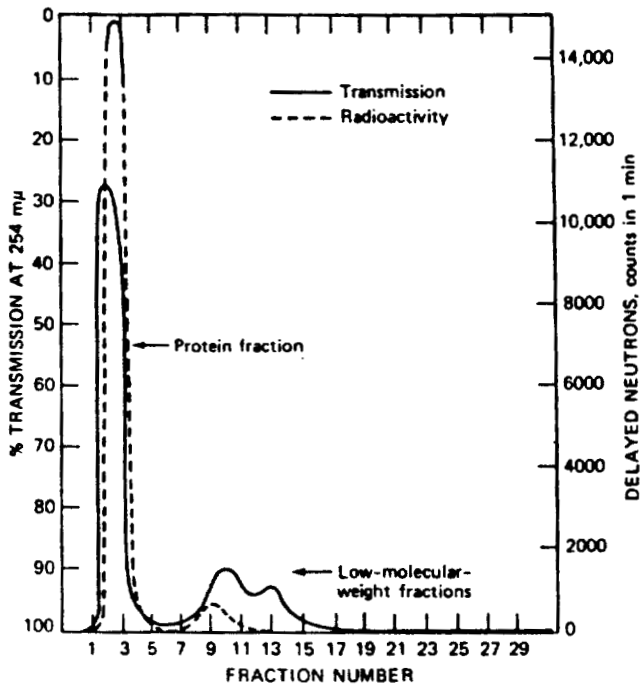


Fig. 5 Demonstration of the association of Pu(IV) with serum proteins in the absence of citrate. Column is 29 by 1.6 cm. Buffer is 0.01M TRIS-HCl in 0.15M NaCl, pH 8.0. Temperature is 4°C. Flow rate is ~30 ml/hr. Volume fraction is ~5 ml. Sample volume applied is ~1.5 mL Reproduced from Popplewell and Boocock (1967) with the permission of the authors and publisher.

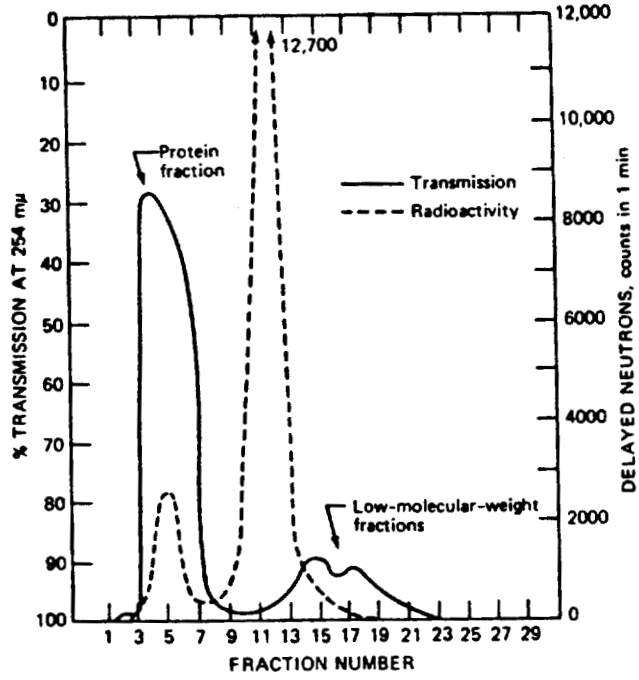


Fig. 6 Demonstration of the dissociation of Pu(IV) from serum proteins in the presence of excess citrate. Column is 30 by 1.6 cm. Buffer is 0.01M TRIS-HCl in 0.15M NaCl and 0.001M sodium citrate, pH 8.0. Temperature is 4°C. Flow rate is ~30 ml/hr. Volume fraction is 5 to 6 mL Sample volume applied is 1 mL Reproduced from Popplewell and Boocock (1967) with the permission of the authors and publisher.

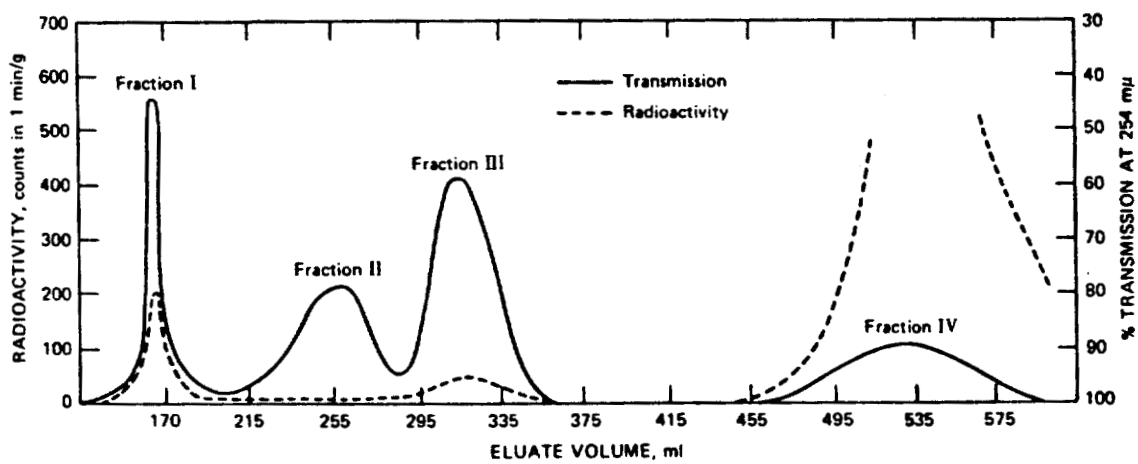


Fig. 7 Demonstration of the dissociation of Pu(IV) from serum proteins in the presence of excess iron. Column is 91 by 2.5 cm. Buffer is 0.1M TRIS-HCl in 1M NaCl, pH 8.0. Temperature is 8°C. Flow rate is 6 to 8 ml/hr. Reproduced from Popplewell and Boocock (1967) with the permission of the authors and publisher.

in which the plutonium radioactivity was associated originally with fraction III, the albumin–transferrin peak. They added iron to the original plutonium transferrin solution. The iron effectively shunted some plutonium away from fraction III to an association with macroglobulins (fraction I), but the bulk of the activity was present unbound in fraction IV.

Next, Popplewell and Boocock (1967) added excess plutonium (Fig. 8; compare with Figs. 3 and 7) and observed the same net effect. The fraction of the plutonium still associated with the transferrin was considerably reduced. They assumed that the binding capacity of the transferrin in their solution had been exceeded, and the excess plutonium was present unbound.

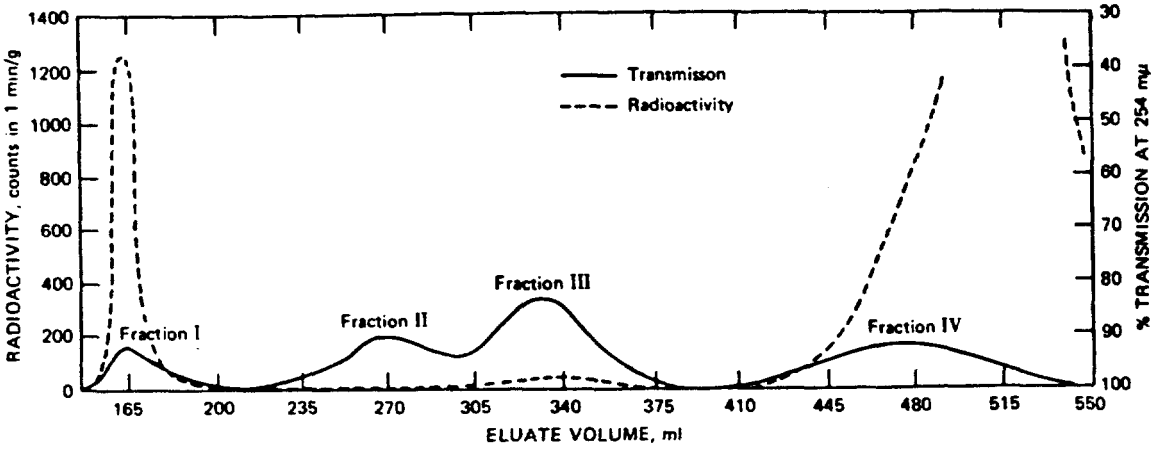


Fig. 8 Demonstration of the saturation of the binding capacity of serum proteins for Pu(IV) in the presence of excess Pu(IV). Column is 94 by 2.5 cm. Buffer is 0.1M TRIS-HCl in 1M NaCl, pH 8.0. Temperature is 3 to 6°C. Flow rate is 9 to 10 ml/hr. Sample applied is 0.2 ml of serum diluted with 3.4 ml of TRIS buffer. Reproduced from Popplewell and Boocock (1967) with the permission of the authors and publisher.

At the University of Utah, Stover et al. (1968) almost simultaneously performed the same kinds of experiments and confirmed the results of Popplewell and Boocock (1967). The findings were extended to human and dog blood. They summarized the findings as follows: plutonium is reversibly bound to transferrin; plutonium occupies the same binding sites that are occupied normally by iron; the plutonium–transferrin complex is not as stable as the iron transferrin entity; uptake of plutonium in bone occurs because the forming red cells reject the plutonium that is transported to them.

These workers, along with Turner and Taylor (1968), also showed that, if one sampled blood from rats or dogs a few hours after plutonium was injected, 95% of the plutonium still in the circulation was transferrin-bound.

Bruenger et al. (1969) also demonstrated that, if the iron-storage protein, ferritin, were added to a test tube containing plutonium bound to transferrin, the plutonium shifted to the ferritin molecules. Using cell homogenization techniques, they also demonstrated that most of the plutonium deposited in dog liver was associated with various forms of ferritin (Stevens et al., 1971). Since then they have shown that, with the passage of time, plutonium is transferred from soluble to insoluble forms of ferritin in the liver of the dog.

These observations led, in a reexamination of the available human data, to an attempt to correlate the deposition and early excretion of plutonium in people with iron-transport mechanisms. It was found (Table 1) that the early excretion of plutonium in urine was less in those persons who were presumed to be anemic and likely to have increased iron-binding capacities. It was also found that the early fecal excretion of plutonium was reduced in those persons in whom gastrointestinal functions were reduced—conditions that also lower fecal iron excretion (Table 2).

These correlations between plutonium and iron behavior in ill human beings are not conclusive—the groups are small and the severities and kinds of the illnesses of the subjects were variable—but, at least they support the use of an iron model as a working hypothesis.

GASTROINTESTINAL ABSORPTION

There have been many animal studies of intestinal absorption of plutonium. We cannot cover them all, but I can point out some general principles about the effects on absorption of the nature of the plutonium compound and the physiological status of the animal to which the plutonium was administered.

Table 3 contains a sampling of the data on plutonium absorption. These studies have been the subject of three recent comprehensive reviews (ICRP, 1972; Vaughan et al., 1973; Buldakov et al., 1969).

The fractional oral absorption value that is in current use by ICRP (1959) and NCRP (1959) is 0.003% and is based on rat and pig studies with Pu(IV) in acid solution given as a single dose or as multiple doses placed directly into the stomach. The plutonium was usually given when the stomach was empty, and it is assumed that these are close to maximum uptake values.

All of these absorption values, with the exception of the Pu(IV) in people, are based on analysis of the tissues and urine. They were not obtained from the difference between 100% and fecal elimination.

It is clear that, if the binding ion were citrate, gastrointestinal absorption was increased. If the plutonium were given as Pu(VI), the absorption was increased. If insoluble plutonium oxide particles were given, the plutonium absorption was substantially reduced. If the animal were very young, plutonium absorption was increased, whether the compound given was the nitrate or the citrate.

Table 1 Influence of Anemia and Impaired Kidney Function on Early Urinary Plutonium Excretion in Man

Case	Red-cell count	Kidney function	Pu in urine, % 1 to 6 days	Pu in urine, % 19 to 24 days
Pu(IV) Citrate				
HP-1	Low	N*	0.670	0.121
HP-2	N	N	1.240	0.104
HP-3	N	N	1.198	0.091
HP-4	N	Ab†	1.264	0.147
HP-5	N	N	0.641	0.117
HP-6	N	N	0.914	0.080
HP-7	Low	N	0.790	0.057
HP-8	N	N	1.038	0.159
HP-9	Low	N	0.479	0.186
HP-10	N	N	1.281	0.108
HP-12	Low	N	0.482	0.173
Pu(VI) Citrate or Nitrate				
Chi-1	Low	Ab	3.072	0.161
Chi-2	Low	Ab	0.503	
Chi-3	?	?	1.231	0.094
Cal-1	Low	N	0.855	0.035
Pu(IV) Citrate Only				
Erythropoietic status			Mean ± Standard deviation	Mean ± Standard deviation
Anemic, No. of cases 4			0.605 ± 0.152	0.134 ± 0.058
Normal, No. of cases 6			1.052 ± 0.236	0.110 ± 0.027
"P"‡			<0.01	>0.5

*N = normal.
†Ab = abnormal; not included in calculated means.
‡T-test of Fisher.

Increased absorption of plutonium by young animals is in agreement with an iron model. During growth, absorption of iron from the gastrointestinal tract is greater than it is in adulthood.

PLUTONIUM INHALATION

Figure 9 is a slightly modified version of the ICRP lung model (ICRP, 1966). The biological half-times and transfer fractions are those for an ideal particle 1 μm AMAD (activity median aerodynamic diameter). Of 100% inhaled, approximately 40% is not deposited in the respiratory tract at all. Approximately 20% is deposited in the nasopharyngeal region (N-P), about 10% in the tracheobronchial region (T-B), and about 30% in the deep lung or pulmonary region (P). The nasopharyngeal and tracheobronchial deposits are quickly cleared via the mucus and ciliary action to the gastrointestinal tract from which they are eliminated in the feces.

In the case of insoluble particles, the deep lung is the only site of real interest—it is the site in which long-term deposits are retained, from which absorbed material passes into the blood, and in which any damage is ultimately done. Some of the initial pulmonary deposit is immediately trapped by mucus and cleared via the mucociliary tree, branch f. The rest of the initial pulmonary deposit either is trapped by phagocytic cells or is absorbed into the body. Some phagocytized material is also eventually eliminated by ciliary action (that is, the slow term, branch g), and some seems to remain fixed until the death of the cells. Some moves intact to other sites, such as pulmonary and other lymph nodes, or is slowly rendered soluble and absorbed.

In Table 4 there is a rough comparison of the pulmonary absorption of various plutonium compounds. The data are given as the fraction of the initial pulmonary burden in the tissues (bone, liver, and soft tissues other than lung) or excreted in urine approximately 3 months after inhalation. In general, for the same particle size, the more soluble the inhaled plutonium compound, the greater will be the absorption from the lung; for example, note the difference between the absorption of plutonium citrate and nitrate and between nitrate and fluoride. The least absorbed compound is the calcined $^{239}PuO_2$.

Note also the substantially greater absorption of an equal microcurie amount of $^{238}PuO_2$. Whether this is the

Table 2 Influence of Restricted Food Intake and Abnormal Digestive Secretion on Gastrointestinal Excretion of Plutonium in Man

	Injected Pu in feces, %	
	1 to 6 days	19 to 24 days
Pu(IV) Citrate		
Normal diet		
HP-2	1.408	0.231
HP-4	1.420	0.164
HP-5	1.031	0.111
HP-6	0.886	0.080
HP-9	1.504	0.324
HP-12	1.700	0.264
Mean	1.325 ± 0.30*	0.196 ± 0.08*
Restricted diet†		
HP-1	0.715	0.064
HP-7	0.544	0.064
HP-8	0.894	0.158
HP-10	0.591	0.072
Reduced liver function		
HP-3‡	0.596	0.066
Mean §	0.668 ± 0.14	0.091 ± 0.04
Pu(VI) Citrate or Nitrate		
Cal-1 (restricted diet)¶	0.324	0.061
Chi-1 (diet not known)**	1.811	0.102

*Underlined means were compared with means immediately below by the Fisher t-test. Single underline $P < 0.01$; double underline $P = 0.05$.

†HP-1 and HP-8 were being treated for peptic ulcers. Restricted diet is assumed for HP-7 and HP-10 because of their severe heart conditions.

‡Probably jaundiced.

§Includes four restricted-diet cases and HP-3 with subnormal liver function.

¶Total gastrectomy on day 4. Little fecal output until day 18.

**Dietary intake may have been voluntarily reduced following mouth surgery on day 2.

Table 3 Absorption of Plutonium Compounds from the Gastrointestinal Tract

Species	Pu compound	Percent of dose absorbed	Reference
	Adult Animals		
Rat	^{239}Pu(VI) nitrate	1.9	Weeks (1956)
Rat	^{239}Pu(IV) citrate	0.03	Weeks (1956)
Dog	^{239}Pu(IV) citrate, pH = 6	0.03	Buldakov (1969)
Rat	^{239}Pu(IV) nitrate, pH = 2	0.003	Katz (1954)
Swine	^{239}Pu(IV) nitrate, pH = 2	0.002	Weeks (1956)
Man	^{239}Pu(IV) chloride, pH = 2	<0.1	Russell (1946)
Rat	^{239}Pu(IV) oxide, fired	5×10^{-5}	Baxter (1971)
Swine	^{238}Pu(IV) oxide, fired	$<10^{-6}$	Smith (1966)
	Young Animals		
Puppy, 3 day	^{239}Pu(IV) citrate	0.7	Buldakov (1969)
Rat, young	^{239}Pu(IV) citrate	0.13–0.43	Mahlum (1967)
Rat, young	^{239}Pu(IV) nitrate, pH = 2	0.1–0.25	Ballou (1958)
Puppy, 3 day	^{239}Pu(IV) nitrate, pH = 2	0.14	Buldakov (1969)

Table 4 Absorption of Plutonium into the Body of the Beagle Dog After Inhalation of Various Compounds

Pu compound	Percent absorbed 90 days after exposure	Reference
^{239}Pu(IV) citrate	~60	Ballou (1972ab)
^{239}Pu(IV) nitrate	35–40	Ballou (1972a)
^{239}Pu(IV) fluoride	5	Dilley (1970)
^{239}Pu(IV) oxide, fired	<1	Bair (1968)
^{238}Pu(IV) oxide, fired	5–10	Park (1970)

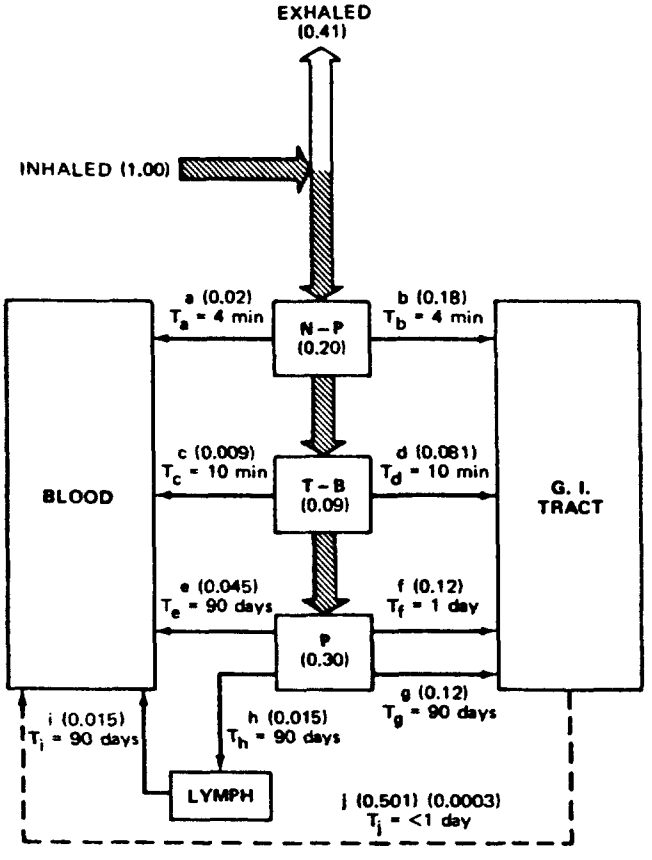


Fig. 9 General inhalation model; parameters shown are for Class W compounds and a particle size of 1 μm AMAD as given in ICRP (1966). Reproduced from Durbin (1973) with the permission of the publisher.

result of (1) disruption of the crystal lattice by alpha self-destruction, (2) radiolysis of the surrounding tissue fluids, (3) local heating, or (4) radiation damage to the surrounding tissues remains to be worked out.

After passage across the lung barrier, the distribution of inhaled plutonium is similar to that observed after injection or ingestion. There is one exception, and this must also be further studied. Apparently some particulate $^{239}PuO_2$ may pass along the lymph-node chain into the circulation from which it is filtered out by the reticuloendothelial cells of the liver and marrow.

ABSORPTION OF PLUTONIUM FROM WOUNDS

Table 5 summarizes the data on absorption of plutonium from subcutaneous implants or from deeply penetrated wounds. In general, the absorption from an intramuscular or subcutaneous site as shown here follows the same pattern as absorption of ingested or inhaled plutonium. Intramuscular plutonium citrate is absorbed within a few hours to a few days. In industrial accidents, plutonium metal fragments or PuO_2 particles have been embedded in wounds, and absorption is nearly undetectable from months to years later.

In man, and presumably in other mammals, about half of the body's transferrin is located in tissue fluid and lymph. Plutonium introduced into muscle or beneath the skin must enter the circulation via the lymph. Even though the transferrin concentration in extracellular fluid is not high, it is reasonable to suppose that plutonium compounds may be slowly solubilized by complex formation with this protein.

PLUTONIUM DISTRIBUTION

Table 6 shows the initial distribution of soluble plutonium in man and several larger laboratory animals. These distributions are about the same as they are in other smaller species. The deposition and retention model in Fig. 1 shows several possible fates for absorbed plutonium: deposition in liver, initially in hepatic cells; deposition on bone surfaces; deposition in other soft tissues (in which the precise associations are not known). However, plutonium has been found associated with kidney stones; the intertubular tissue of the renal cortex; at sites of ectopic calcification in the aorta and tracheal cartilages of older animals; and in normal iron-storage sites such as the spleen. One other possible fate is excretion, but excretion is not a large factor in human exposure.

In Table 6 note the two versions of the human data. One (all 7 cases) is from Langham et al. (1950), in which it was assumed that the plutonium in bone was uniformly distributed.

The more recent calculations (5 males only) are based on a nonuniform skeletal deposition of plutonium using

Table 5 Absorption of Plutonium Compounds After Intramuscular or Subcutaneous Injection

Species	Nuclide and compound	Dose, μg	Days after injection	Percent of dose absorbed	Reference
		Intramuscular Injection			
Monkey	^{238}Pu(IV) citrate, pH = 3.5	0.3	0.08	69	Durbin (unpublished)
Dog	^{239}Pu(VI) citrate	6800	15	98	Painter (1946)
Rat	^{238}Pu(IV) nitrate, pH = 1.5	0.2	90	98	Nénot (1972)
Rat	^{238}Pu(VI) citrate	<0.1	15	76	Hamilton (1953)
Rat	^{239}Pu(VI) chloride, pH = 2.5	15	64	65	Scott (1944)
Rat	^{239}Pu(III) chloride, pH = 2.5	15	64	61	Scott (1944)
Rat	^{239}Pu(IV) nitrate, pH = 2.5	15	64	32	Scott (1944)
Rat	^{239}Pu(IV) nitrate, pH = 1.5	242	90	25	Nénot (1972)
		Subcutaneous Injection			
Rat	^{239}Pu(VI) chloride, pH = 2.5	15	16	58	Scott (1944)
Piglet	^{239}Pu(IV) citrate, pH = 6.5	3500	16	>44	Buldakov (1967)
Rat	^{239}Pu(IV) nitrate, pH = 2.5	15	16	34	Scott (1944)
Swine	^{239}Pu(IV) nitrate, 2N	16–80	7	7.2	Cable (1962)
Dog	^{239}Pu(IV) oxide, fired	87	365	0.27	Johnson (1972)

Table 6 Initial Distribution of Plutonium in Larger Animals Injected with Pu(IV) Citrate

Reference*	Stover–Baxter	Durbin	Buldakov	Bustad–Clarke	Langham Man	
Species	Dog	Monkey	Sheep	Swine	All 7	5 males
Age, years	1.5	>12	0.6	1.5	60	63
Dose, μCi	3–30	8		5	0.3	0.3
Isotope	239	238	239	239	238–239	238–239
Days after injection	6–22	8	32	30	5–457	5–457
			Percent of injected dose			
Skeleton	54	31	~43†	72	66†	37–45†
Liver	31	47	13	13	22	23–43
Spleen	0.3	0.2	0.1	8.3	0.4	0.4
Kidneys	0.4	1.0	0.2		0.3	0.2
Lung	0.2	0.3	0.2		1.0	1.1
Muscle	1.2	4.3	1.7		6.2	7.3
Excreted	12	7.1		6	5.4	6.3

*Baxter et al. (1973); Buldakov et al. (1969); Bustad et al. (1962); Clarke et al. (1959); Durbin (unpublished); Langham et al. (1950); Stover et al. (1959).

†Skeleton estimated from a sampling of bones.

intraskeletal distributions in the dog and the monkey. The amount of plutonium was greater in the livers and less in the skeletons of the long-lived animals that were skeletally mature at the time of plutonium injection (man and monkey) than of those animals that still exhibited some bone-growth activity (Beagle dog, swine, and probably sheep).

The soft tissues of the three largest species (swine, sheep, and man) contained more plutonium than those of the smaller species. It is clear from Fig. 10 that the soft-tissue compartment in the human cases declines, but it is always larger than in the dogs. Soft tissue—that is, nonliver—plutonium seems to be eliminated from the soft tissue, but most of it is not eliminated from the body. It is recirculated to the bone and the liver.

Both the differences in the amounts and clearance rates of the soft tissues and the fractionation of plutonium between liver and bone vary with age in animals other than

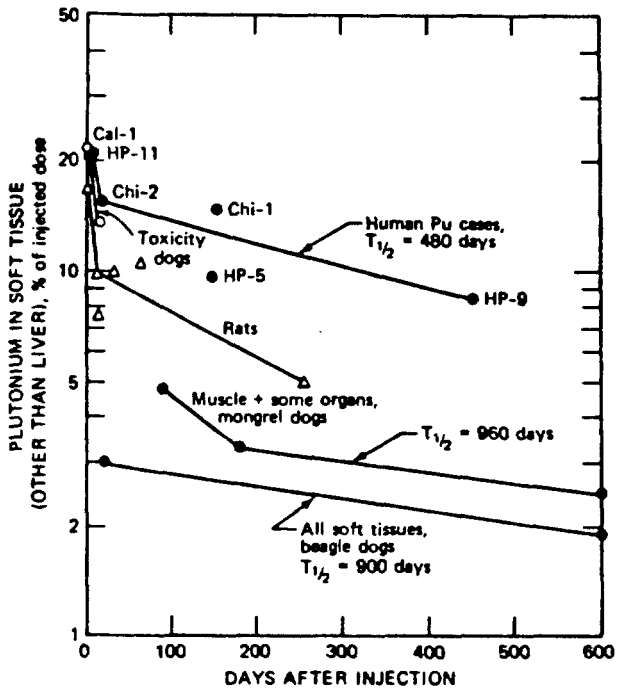


Fig. 10 Clearance of plutonium from soft tissues. Reproduced from Durbin (1972) with the permission of the publisher.

rodents. In adults, soluble plutonium is distributed 31 to 45% in the skeleton, 47 to 23% in the liver, and 12 to 23% in soft tissues; in growing animals, plutonium distribution is 43 to 72% in bone, 31 to 13% in liver, and 3 to 8% in soft tissues.

This bone and liver distribution pattern is also found for scandium and yttrium, the rare earths, and the trivalent actinides. The quantitative variations appear to depend on ionic size and the stability of complexes. A common distribution pattern among chemically similar elements suggests that all participate in a common transport and storage system. For the sake of argument, I have chosen the iron-transport system. Liver is a principal iron-storage organ. At normal levels of iron loading of transferrin, liver accumulation of transferrin-bound iron appears to be small.

Bone accumulation of the multivalent cations is not easy to explain. Although ferric iron can be adsorbed onto calcium phosphate, free iron is not a normal bone constituent. Chemical analysis of bone shows that the iron can be completely accounted for by trapped red cells. However, the bones do cover the marrow, and the circulations of the marrow and of trabecular bone are identical. It has been postulated that the plutonium transported to the marrow by transferrin is released at the surfaces of developing red cells and is rejected. The trabecular bone surfaces are sufficiently close so that the plutonium need only diffuse a few microns to encounter a mineralized surface. Calcium phosphate has an enormous capacity to bind multivalent cations. Although bone proteins may play a role in plutonium binding, the amount of mineral available to which the plutonium can adsorb is overwhelming.

DEPOSITION OF PLUTONIUM IN LIVER

The illustrations in this and the next section were presented by the University of Utah group; by Cochran et al. (1962), liver, and by Arnold and Gee (1962), bone, at the first Hanford Symposium on Transuranium Elements.

Soluble plutonium taken up by the liver is initially distributed uniformly as single atoms as shown by the single tracks in Fig. 11. The dark globes are cell nuclei; unfortunately the tracks have been obscured in the reproduction. Subcellularly in the liver, the plutonium is in the hepatic cells associated with the iron-storage protein, ferritin. It is present initially in a relatively soluble state in the cytoplasm of the hepatic cells and can be extracted from them.

With the passage of time, the ferritin molecules accumulate additional iron and become insoluble. As the hepatic cells either die normally or are damaged by the radiation, plutonium-containing ferritin is released as part of the cellular debris. This debris is then taken up by neighboring phagocytic cells, or it enters the circulation, recirculates, and is taken up again by new cells in the liver, closer to the origin of the liver circulation. Figure 12 is a section and autoradiograph from the liver of a high-dose plutonium dog that died 1576 days after injection, and it shows nonuniform collections of plutonium aggregates.

Figure 13 is a lower-magnification autoradiograph from another high-dose dog that died 1324 days after injection. This is an X-ray film autoradiograph, and all the blackening is autoradiograph, not cells. It shows areas of intense plutonium localization not in hepatic cells but in connective tissue and phagocytes in the connective tissue. This nonfunctional tissue surrounds nearly plutonium-free nodules of new hepatic cells.

PLUTONIUM DEPOSITION IN BONE

Bone has probably received more attention than any other tissue with respect to plutonium uptake. Bone-marrow damage is the underlying cause of acute plutonium-induced mortality. Bone tumors were the first-noted and are the best-documented aspect of the pathology of chronic plutonium burdens.

Bone uptake of plutonium is not limited to mammals. Any creature, invertebrate or vertebrate, which contains calcium phosphate or calcium carbonate structures and which grows either a shell, an exoskeleton, or an endoskeleton accumulates plutonium in these mineralized materials. Among invertebrates, the shell may contain up to 90% of the body plutonium. In cartilagenous fishes, the plutonium concentration in the skeleton is about 20 times that in other parts of the body. In bony fishes, the skeletal concentration is about 150 times that in other body parts. Plutonium has not been studied in amphibians, but about 20% of a related element, cerium, is accumulated in the frog skeleton. In chickens the lanthanide rare earths are

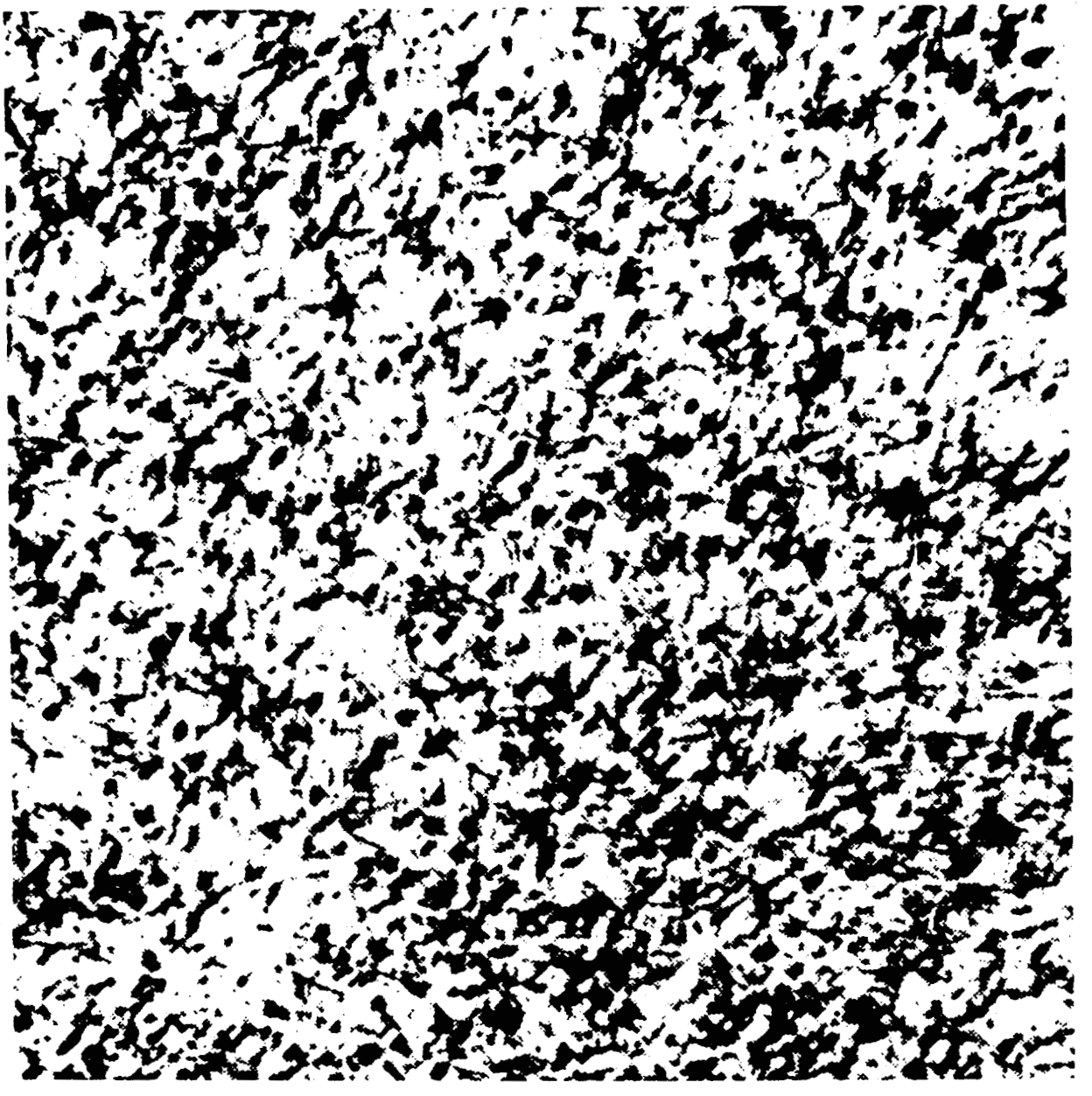


Fig. 11 Detailed autoradiograph showing initial uniform distribution of ^{239}Pu in the liver of P-5 animal sacrificed 24 hr postinjection. Medium magnification. Reproduced from Cochran et al. (1962) with the permission of the authors and the Health Physics Society.

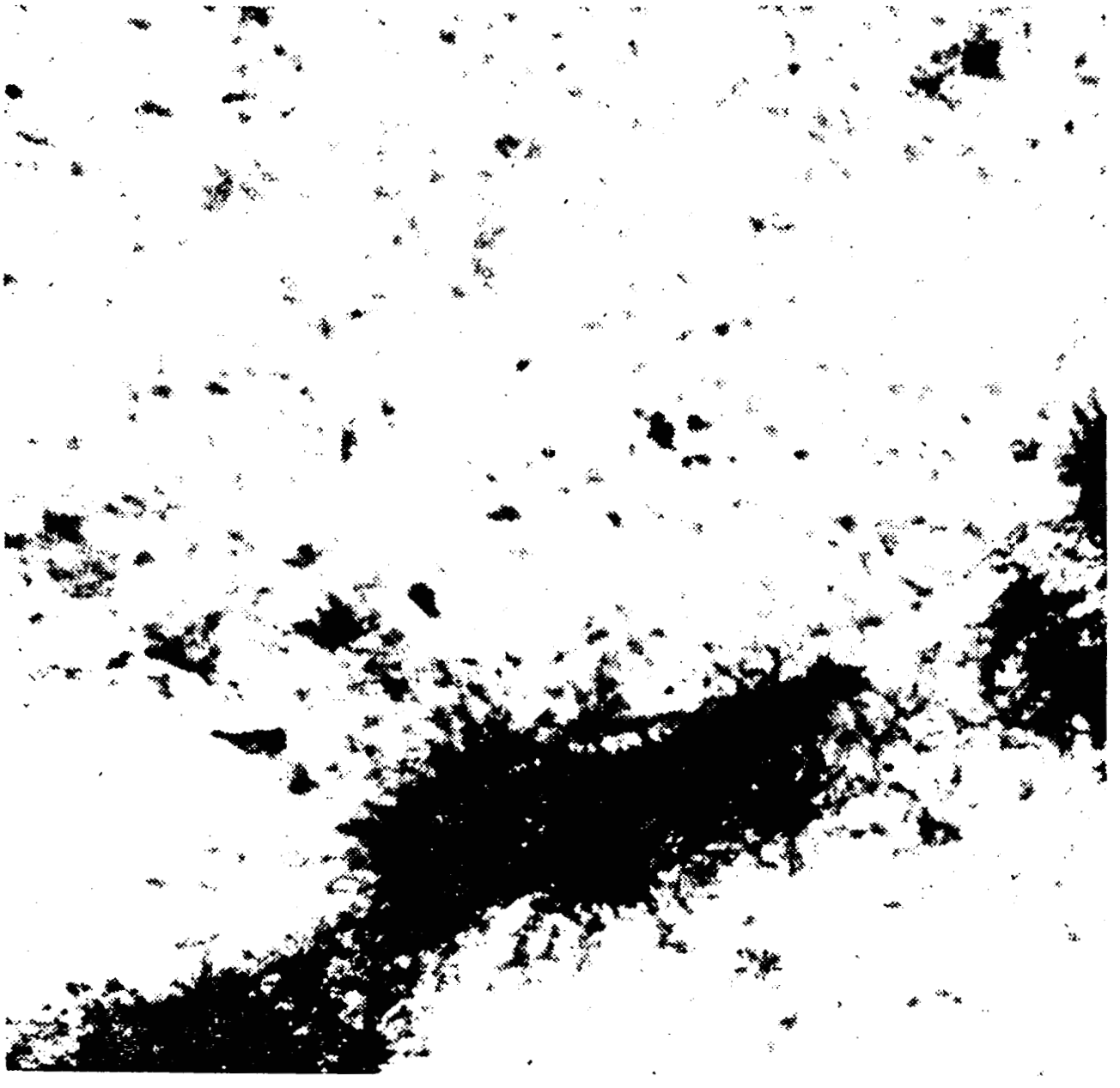
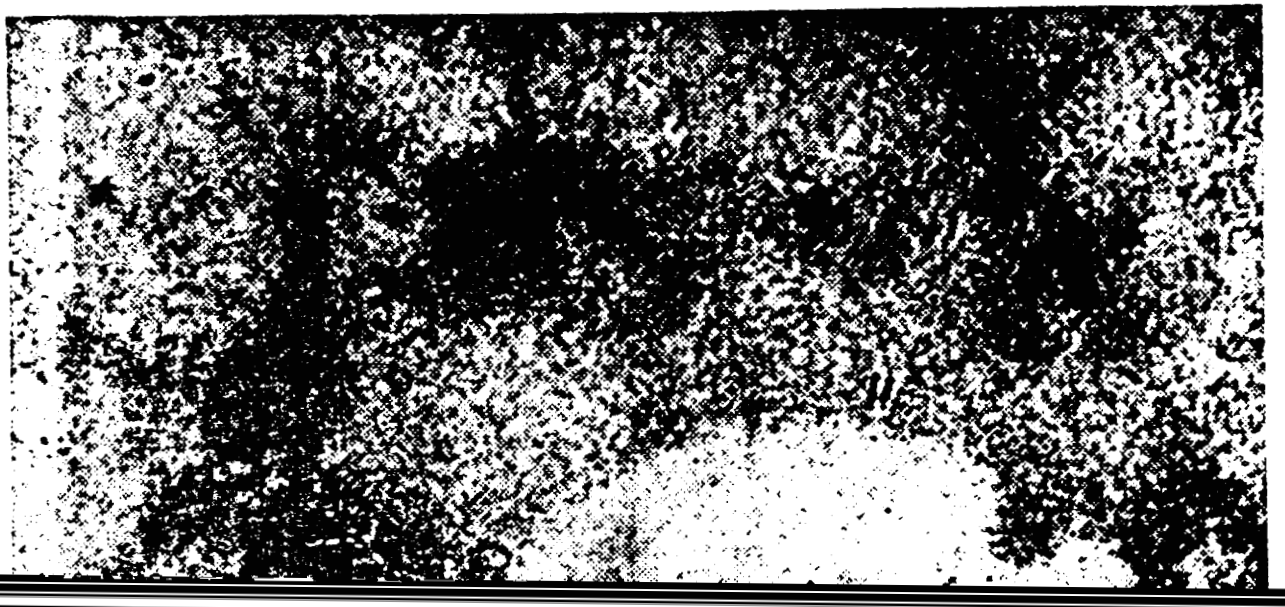


Fig. 12 Detailed autoradiograph showing nonuniform distribution of ^{239}Pu in the liver of P-5 dog sacrificed 1576 days postinjection. Medium magnification. Reproduced from Cochran et al. (1962) with the permission of the authors and the Health Physics Society.



found in the skeleton to the extent of 40 to 70% of the injected dose.

Figure 14 is an historic slide. This was one of the first autoradiographs of plutonium in bone made in Berkeley in 1944 by Axelrod-Heller, Copp, and Hamilton. (See Scott et al., 1948.) It is of the femur of an adult rat that was given plutonium by intramuscular injection and killed 8 days later. The contact autoradiograph is above; below is the section of bone from which it was made stained with hematoxylin and eosin.

They found two remarkable things: (1) the intensity of the labeling in the area close to the circulation was much greater than that in the outside covering or periosteum of the bone, and (2) there was not any plutonium in the body of the bone, as had been demonstrated for radium.

The original materials are still available in our slide files, and not too long ago we took a look at some of them. It is remarkable that they were able to get such accurate results since the preparations were crude and the bone sections are shredded, torn, and cracked - they look about the same as they do in these pictures.

In bone, plutonium initially deposits upon the barest surfaces, those with the thinnest cellular coverings, which are closest to the circulating blood and to the sites of active red-cell production. Figure 15 is a section of the costochondral junction (the junction between bone and cartilage in rib) taken from a dog 24 hr after plutonium injection. Note that the interior surfaces (endosteal) are very dark, and the surface just below the soft tissue covering (periosteum) as we saw in rat bone is much fainter. Figure 16 is a higher magnification of a trabeculus from one of the vertebrae of the same dog, and it shows trabeculae surrounded by active marrow. Plutonium tracks cover almost the entire surface of the trabeculae.

Even in adult animals, bone surfaces are not static, and in these young adult dogs there is a great deal of bone remodeling. Existing bone is removed; new bone is deposited on old surfaces; and new trabeculae are formed altogether.

The vertebral trabeculus shown in Fig. 17 was taken from a dog 1200 days after injection of a fairly low dose of plutonium, 0.1 μCi/kg. It shows the original plutonium deposit, the heavy furry lines, and new bone which was subsequently laid down on top of that. The new bone contains diffusely distributed plutonium. Bone always has some surface, and, if new bone is continually deposited on top of old surfaces, eventually one sees what looks like a generalized diffuse distribution.

The surface of the trabeculus that existed at the time the animal was killed (lower right) evidently has been present for some time, because it has a fairly high concentration of alpha tracks. All of the plutonium that has arrived in this bit of bone since the time of the injection has been recycled through the blood. Plutonium deposited in other tissues and plutonium deposited on bone surfaces which have been resorbed is returned to the circulation, and this, in turn, is partly recycled back into the skeleton.

Figure 18 shows a trabeculus that was formed entirely in the 4 years after the injection of 0.3 μCi/kg of Pu(IV); it is composed of diffusely labeled bone and has only a light surface deposit. Figure 18 also shows the presence of aggregates of plutonium in the marrow. The aggregates are inside phagocytic cells, and the plutonium in them was once on bone surfaces. The bone surfaces were resorbed; and, presumably, the resorbed plutonium could not be completely solubilized and was taken up as particulate material. This phenomenon seems to be dose and/or time related. Six or more years after a lower dose (0.1 μCi/kg), we see in Fig. 19 diffusely labeled postinjection bone with a smaller number of phagocytes containing smaller amounts of unsolubilized plutonium.

Figure 20, the last in this sequence, was taken from the same anatomical region as the first slide in the series. The dog received a large plutonium dose, 2.7 μCi/kg, and died 500 days later. All the bone above the dark arrow on the right was formed after the injection. Most of it is diffusely labeled, and some of it has obviously acquired some rather substantial accumulations. At the original growth site (the dark arrow), normal processes of bone removal have been disrupted, permitting the old heavily labeled bone to persist.

Prolonged retention of plutonium in bone seems to be the result of at least two processes: (1) retention of the initial plutonium deposit on bone surfaces whether they remain or are buried by new bone and (2) the continuous accumulation of plutonium recirculated from remodeled bone or from other body sites.

PLUTONIUM RETENTION

The reasons why plutonium and related elements remain in the body so long include the following: (1) they circulate in the blood complexed by molecules which are too large to be filtered by the kidney; (2) both bone structures and liver cells are apparently quite long-lived; (3) plutonium in liver is associated with a stable compound that is ordinarily not disturbed unless there is stress on the body's iron stores; and (4) the multivalent cations are apparently caught up in a transport and storage system, the basic purpose of which is to prevent loss and promote reuse. Thus, even when labeled liver cells or bone surfaces die or are changed, their label is recycled and redeposited.

Plutonium retention has not been directly measured in human beings. One can calculate, from the excretion data, a retention half-time of about 200 years for whole-body plutonium as was done by Langham et al. (1950) using the data in Fig. 21. How liver and skeleton each contribute to the overall retention is still not known.

For human bone, estimated biological half-times range from 35 years (based on the kinetics of bone surfaces and 60% plutonium redeposition in bone) to 200 years (origi-

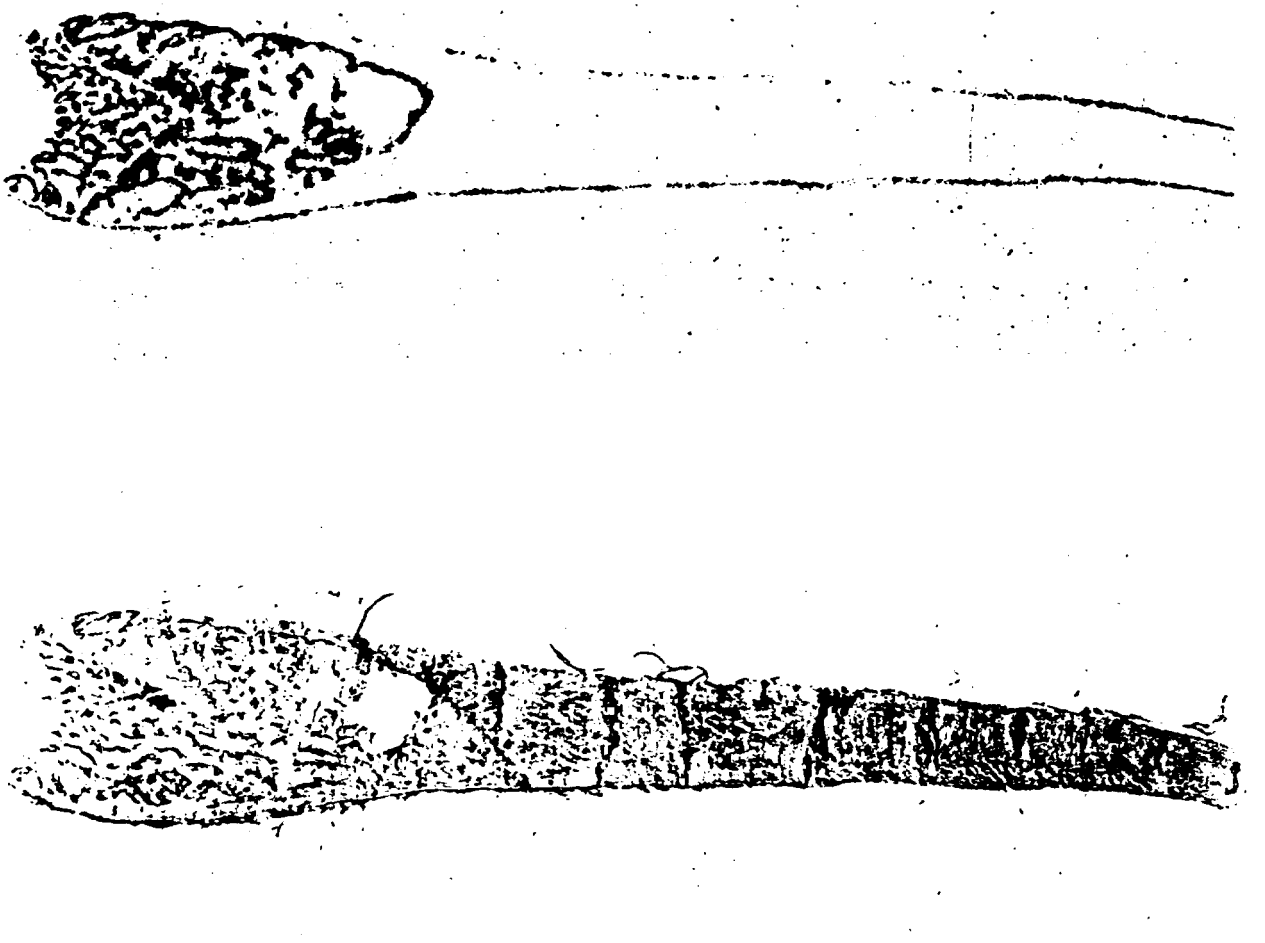


Fig. 14 Contact autoradiograph on no-screen X-ray film (upper image) and section of undecalcified rat bone (distal femur) from which it was made stained with hematoxylin and eosin; adult rat killed 8 days after intramuscular injection of ^{239}Pu(IV) chloride, pH = 3. Prepared by D. J. Axelrod and J. G. Hamilton; previously unpublished.

nally estimated by Langham). Recently, an ICRP Task Group published an estimate of plutonium half-time in human bone of 100 years (implying 85% redeposition of circulating plutonium in bone).

Estimates of the half-time of plutonium in human liver range from 40 years (the ICRP Task Group, based on extrapolation from animals) to no loss at all (implied by the short half-time in bone and a 200-year half-time in the whole body as illustrated in Fig. 22). The value in current use by the ICRP and NCRP is 90 years.

BEHAVIOR OF TRIVALENT ACTINIDES

In Table 7 and Fig. 23 from Durbin (1960, 1962), the initial distributions of plutonium in rats are compared to the distributions of other actinide elements which were available for study as of 1960. The valences were as follows: Pu(IV), Am(III), Cm(III), Th(IV), U(II), and, presumably, Np(V). Bone uptake was greatest for Pu(IV) and Th(IV) and least for U(II). Liver deposition was greatest for the trivalent actinides.

In Fig. 23 are compiled early metabolic data for the entire lanthanide sequence and for the actinides through californium. (Data shown here are for Pu(IV), Th(IV), Pa(V), and Np(V); all others are in the III state.) It shows that bone deposition is favored for ions of the same electrical charge as their size declines and that the reverse, deposition in the liver, is favored in the case of larger ions. It appears at the moment (unless there is some other candidate available) that the most sensitive system that might be responsible for these large shifts accompanying

(Text continues on page 53.)

Fig. 15 Contact radioautogram of costochondral junction demonstrating the heavy endosteal deposition and irregular lighter vascular and periosteal deposition in dog sacrificed 24 hr after ^{239}Pu injection. Reproduced from Arnold and Jee (1962) with the permission of the authors and the Health Physics Society.

Fig. 16 Detailed radioautogram of trabeculus from the vertebral body of an animal sacrificed 24 hr after ^{239}Pu administration. The point of origin of the tracks corresponds to the endosteal surface separating the bone and marrow. Reproduced from Arnold and Jee (1962) with the permission of the authors and the Health Physics Society.

Fig. 17 Detailed radioautogram from the vertebra of a 0.1 μc/kg animal sacrificed 1200 days after ^{239}Pu injection. The dense wavy line represents the deposition at the original endosteal border; the bone below formed after injection contains a diffuse distribution of alpha activity, whereas the bone deposited before injection is free of activity. Reproduced from Arnold and Jee (1962) with the permission of the authors and the Health Physics Society.

Fig. 18 Detailed radioautogram of trabeculus and marrow from vertebra of 0.3 μc/kg animal showing diffuse alpha distribution in bone; large stars in marrow indicate the local concentration of ^{239}Pu resorbed from bone. Reproduced from Arnold and Jee (1962) with the permission of the authors and the Health Physics Society.

Fig. 19 Trabeculus and marrow from vertebra of 0.1 μc/kg animal demonstrating the diffuse distribution in bone but the lack of intense macrophage concentration in the marrow. Reproduced from Arnold and Jee (1962) with the permission of the authors and the Health Physics Society.

Fig. 20 Contact radioautogram of end of rib of 2.7 μc/kg animal sacrificed 500 days postinjection showing (arrow) site of growth line at time of injection. All bone above this was deposited after injection and contained both diffuse distribution and secondary endosteal or surface deposition of ^{239}Pu from recycling ^{239}Pu in the blood. Reproduced from Arnold and Jee (1962) with the permission of the authors and the Health Physics Society.

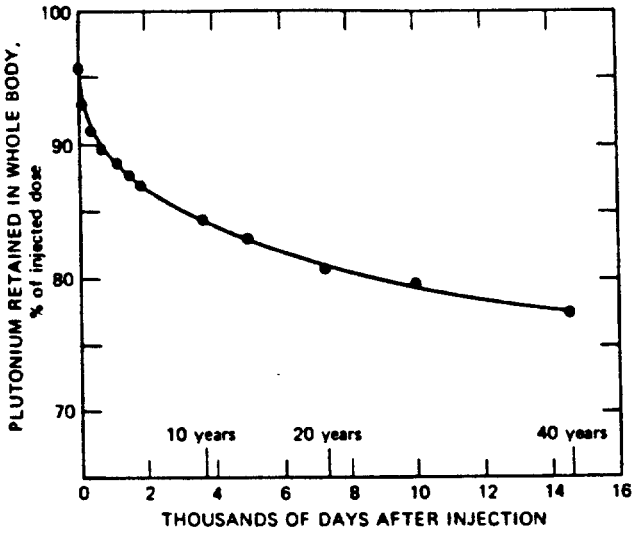


Fig. 21 Whole-body retention of ^{239}Pu in man. Calculated using Langham et al. (1950) excretion equation. Reproduced from Durbin (1971).

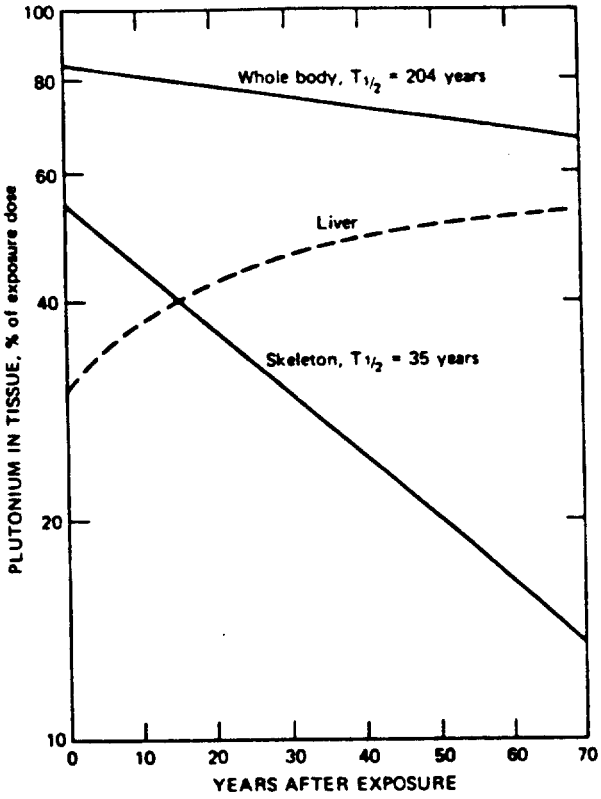


Fig. 22 Calculated retention of ^{239}Pu in the human liver and skeleton. Reproduced from Durbin (1971).

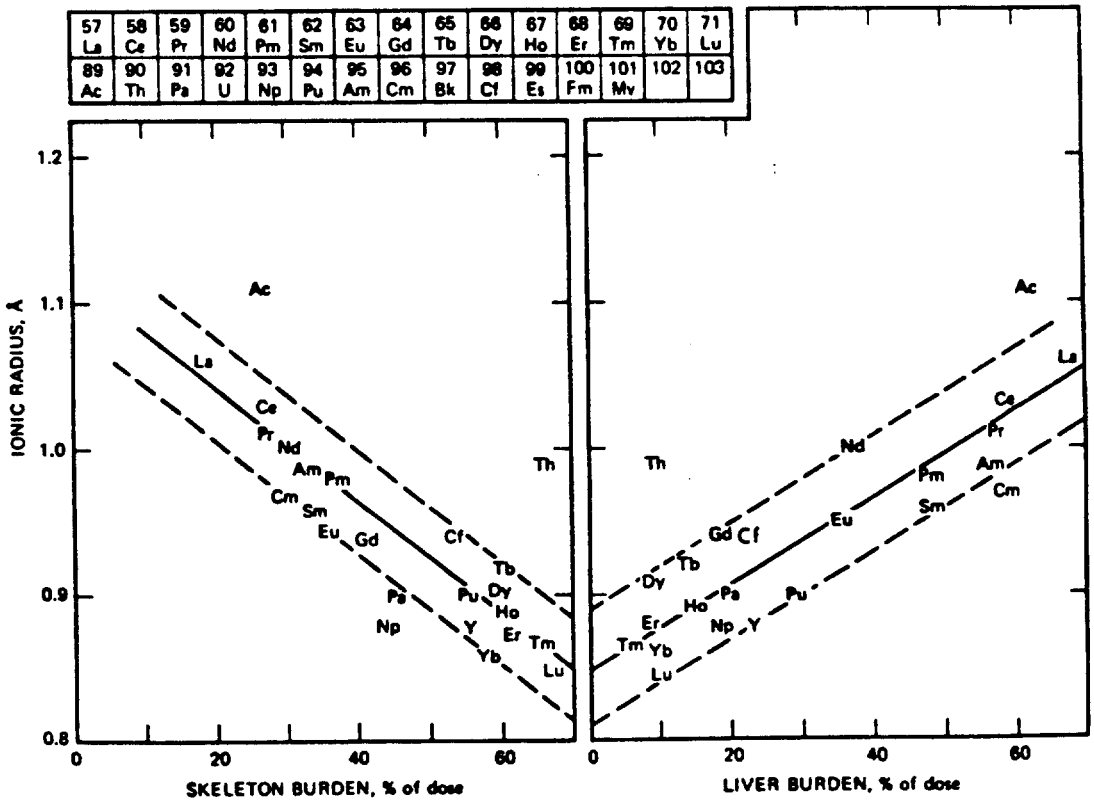


Fig. 23 Initial deposition in the liver and skeleton of the rat of multivalent lanthanides and actinides; and the influence of ionic radius. Reproduced from Durbin (1962) with the permission of the Health Physics Society.

Table 7 *Distribution of Radioisotopes of the Actinide Elements in Various Tissues of the Rat After Intramuscular Injection*

Radioisotope	Chemical form administered	Time, days	Percentage of absorbed dose			
			Bone	Kidney	Liver	Excreta
^{227}Ac	Ac (citrate)	4	26.8	0.6	56.4	10.6 U + F
^{237}Th	Th (citrate)	8	66.3	3.3	4.1	14.8 U + F
^{230}Pa	*	4	45.1	4.0	7.8	24.6 F
^{230}U	UO_2Cl_2	4	10.9	11.8	0.2	76.0 U
^{237}Np	†	1	44.4	2.6	8.5	36.9 U
^{239}Pu	PuO_2Cl_2	4	70.9	1.8	8.4	8.2 F
^{241}Am	$AmCl_3$	4	19.1	2.3	35.7	34.7 F
^{243}Cm	$CmCl_3$	4	29.0	1.6	40.2	20.0 F

*Chemical form unknown but oxidation state probably 4+ or 5+.
†Administered in concentrated NH_4Cl and Na citrate; oxidation state 4+ or 5+.

the very small changes in ion size are the stabilities of the transferrin complexes.

We look into the future for tests of the ion model; experiments with real materials; an examination of the age-related variations of plutonium metabolism; the extension of metabolic and toxicological study to additional species; and the continued follow-up of human beings who have been exposed to plutonium.

DISCUSSION BY ATTENDEES

Dr. W. R. Stratton: Thank you. Are there questions?

Speaker: Have you been doing any experimenting with compounds removed from these animals?

Dr. P. W. Durbin: Actinide removal is such a large subject field, it warrants a talk all by itself. At the moment DTPA is the treatment of choice. Use of DTPA was reviewed recently by Vaughan.

Dr. Stratton: Thank you. Are there other questions?

Dr. K. Z. Morgan: As you know, the present levels in the handbooks of NCRP and ICRP are based on the very crude assumption of uniform distribution of these actinides, and so on, in the skeleton. The decision was made recently by ICRP Committee II to make the calculations in the new handbooks on the dose to the endosteal and periosteal tissues of the trabecular bone. However, from our experience with thorium, which behaves somewhat like plutonium, and from data such as you showed here, for example, the ratio of deposition in the liver to that in the bone seems to increase with time, I noticed in your slide.

Dr. Durbin: Dr. Morgan is referring to Fig. 22, which is only hypothetical. The changes in partition of plutonium between liver and bone in man with the passage of time can only be guessed. It is like a black box—we have a notion about retention of plutonium in the whole body but not about its retention in the separate body parts.

Dr. Morgan: This, though, makes some of us ask, are we getting into a third stage in our calculations? Perhaps even the new generation of calculations that will be published this year are very much out of date already. And maybe for chronic exposure, such as was the case with thorium, it is the liver that is the critical tissue. With the leakage from the pulmonary lymph nodes into and out of the reticuloendothelial system, perhaps some of the material is in a polymeric form and gets into the liver. It may be that hepatic tumors will be the real risk for chronic exposures. Is that a possibility?

Dr. Durbin: Well it appears to be from the dog experiments with inhaled $^{239}PuO_2$. For soluble plutonium, liver is probably an additional critical tissue. However, in the dogs, liver pathology is low at the lower plutonium dose levels, at which bone tumors still occur in large numbers. This would suggest that, although liver should be taken into account, we should not shift from bone as the critical organ. Liver is an additional problem, for which risk perhaps ought to be calculated in a combined way.

I would like to consider the problems of chronic and acute exposure. It would be my prediction, based on the available evidence of microscopic distributions, that, with the passage of time or repeated exposures, we will observe a more generalized bone distribution (see Fig. 19). In the absence of knowledge about the life-spans of human trabeculae, we would be wise to keep using a uniform dose.

As you know, I am not a fan of the endosteal-tissue dose-calculation approach. It seems likely in the environmental case that we are not going to be protecting the adult worker, but perhaps the 10-year-old child whose skeleton is only half finished. In the young person a diffusely labeled skeleton seems more likely, especially for chronic exposure. We do not know the number of trabeculae or the trabecular surface in a 10-year-old child. We know little or nothing about the changes in total trabecular surface from childhood through adulthood to old age. There are so many

unknowns that we are probably better off staying with the uniform dose.

Dr. Stratton: Are there other questions?

Mr. Kressin: I was wondering why you felt that Pu(VI) was absorbed into the body faster than Pu(IV). The reason I ask is because of the high oxidation potential for Pu(VI), and I am wondering how long it stays in that form in the body.

Dr. Durbin: From what we know about plutonium solution chemistry—and here the solution is exceedingly dilute and contains a lot of very peculiar things—Pu(VI) does not exist as such for very long.

The empirical indications are: Pu(VI) is absorbed better from wound sites, from the gastrointestinal tract, and from the lung; and, if Pu(VI) is introduced directly into the circulation, there is less chance of intravascular colloid formation. These observations suggest that Pu(VI) exists long enough to exhibit some absorption and transport characteristics which are a little different from Pu(IV). What the situation is later on, we do not know, but it probably involves reduction to Pu(IV). Certainly, at the pH of the body, at biological salt concentrations, and in the presence of the kinds of ions in mammalian tissue fluids, Pu(IV) is the most stable state.

REFERENCES

Arnold, J. S., and W. S. S. Jee: Pattern of Long-Term Skeletal Remodeling Revealed by Radioautographic Distribution of ^{239}Pu in Dogs, *Health Phys.*, 8: 705-707 (1962).

Bair, W. J., and J. F. Park: Comparative Disposition of Four Types of Plutonium Dioxides Inhaled by Dogs, in *Proceedings of the First International Congress on Radiation Protection*, W. S. Snyder et al. (Eds.), Pt. 1, pp. 181-197, Pergamon Press, Oxford (1968).

Ballou, J. E., Effects of Age and Mode of Ingestion on Absorption of Plutonium, *Proc. Soc. Exp. Biol. Med.*, 98: 726-727 (1958).

——, and J. F. Park, The Disposition of Ingested, Injected, and Inhaled ^{239}Pu Citrate and ^{239}Pu Nitrate, Battelle Pacific Northwest Laboratory Annual Report BNWL-1650(Pt.1), pp. 146-152 (1972a).

——, J. F. Park, and W. G. Morrow, Metabolic Equivalence of Ingested, Injected, and Inhaled ^{239}Pu Citrate, *Health Phys.*, 22: 857-862 (1972b).

Baxter, D. W., M. W. Rosenthal, J. J. Russell, E. Moretti, D. Chaldek, and A. Lindenbaum, Comparison of Monomeric and Polymeric Plutonium in the Dog and Mouse, *Radiat. Res.*, 54: 556-565 (1973).

——, and M. F. Sullivan, Unpublished data cited by W. J. Bair, Toxicology of Plutonium, *Advan. Radiat. Biol.*, 4: 255-315 (1974); Table II.

Bruenger, F. W., B. J. Stover, W. Stevens, and D. R. Atherton, Exchange of ^{239}Pu(IV) Between Transferrin and Ferritin in Vitro, *Health Phys.*, 16: 339-340 (1969).

Buldakov, L. A., E. R. Lyubchanskii, Yu. I. Moskalev, and A. P. Nifatov, Problemi Toksikologii Plutoniya, Atomisdat, Moscow (1969). English Translation: LF-tr-41.

——, A. P. Nifatov, N. M. Tolochkova, and I. I. Burov, Absorption of Plutonium-239 Through the Skin and from the Subcutaneous Tissue of Young Pigs, *Radiobiologiya*, 7: 591-601 (1967). English Translation AEC-tr-6889.

Bustad, L. K., W. J. Clarke, L. A. George II, V. G. Horstman, R. O. McClellan, R. L. Persing, L. J. Seigneur, and J. L. Terry, Preliminary Observations on Metabolism and Toxicity of Plutonium in Miniature Swine, *Health Phys.*, 8: 615-620 (1962).

Cable, J. W., V. G. Horstman, W. J. Clarke, and L. K. Bustad, Effects of Intradermal Injections of Plutonium in Swine, *Health Phys.*, 8: 629-634 (1962).

Clarke, W. J., J. R. McKenney, V. G. Horstman, L. J. Seigneur, J. L. Terry, and L. K. Bustad, Plutonium Metabolism in Miniature Swine, Hanford Biology Research Annual Report HW-59500, pp. 54-60 (1959).

Cochran, T. H., W. S. S. Jee, B. J. Stover, and G. N. Taylor, Liver Injury in Beagles with ^{239}Pu: Distribution, Dosage, and Damage, *Health Phys.*, 8: 699-703 (1962).

Dilley, J. V., Effect of DTPA on Inhaled $^{239}PuF_4$ in Beagles, Battelle Pacific Northwest Laboratory Annual Report BNWL-1050(Vol. 1, Pt.1), pp. 5.14-5.17 (1970).

Durbin, P. W., Metabolic Characteristics Within a Chemical Family, *Health Phys.*, 2: 225-238 (1960).

——, Distribution of the Transuranic Elements in Mammals, *Health Phys.*, 8: 665-671 (1962).

——, Plutonium in Man: A Twenty-Five Year Review, University of California Lawrence Radiation Laboratory Report UCRL-20850 (1971).

——, Plutonium in Man: A New Look at the Old Data, in *Radiobiology of Plutonium*, B. J. Stover and W. S. S. Jee (Eds.), pp. 469-530, The J. W. Press, Department of Anatomy, University of Utah, Salt Lake City, Utah (1972).

——, Metabolism and Biological Effects of the Transplutonium Elements, in *Handbook of Experimental Pharmacology*, Vol. 36, Uranium. Plutonium. Transplutonic Elements, H. C. Hodge, J. N. Stannard, and J. B. Hursh (Eds.), pp. 739-896, Springer-Verlag, Berlin (1973).

——, N. Jeung, and M. H. Williams, A Study of the Relationship Between Behavior of Bone-Seeking Elements and Bone-Growth Status, in *Delayed Effects of Bone-Seeking Radionuclides*, Proceedings of a Conference, Sun Valley, Idaho, 1967, C. W. Mays et al. (Eds.), pp. 137-156, University of Utah Press, Salt Lake City, Utah (1969).

Hamilton, J. G., and K. G. Scott, Effect of Calcium Salt of Versene Upon Metabolism of Plutonium in the Rat, *Proc. Soc. Exp. Biol. Med.*, 83: 301-305 (1953).

International Commission on Radiological Protection, Report of Committee 2 on Permissible Dose for Internal Radiation, *Health Phys.*, 3: 1-380 (1959).

——, Deposition and Retention Models for Internal Dosimetry of the Human Respiratory Tract, Task Group on Lung Dynamics, P. E. Morrow (Chairman), *Health Phys.*, 12: 173-207 (1966).

——, The Metabolism of Compounds of Plutonium and Other Actinides, Task Group of Committee 2, A. Lindenbaum (Chairman), ICRP Publication 19, Pergamon Press, Oxford (1972).

Johnson L. J., R. L. Watters, J. L. Lebel, C. R. Lagerquist, and S. E. Hammond, The Distribution of Pu and Am: Subcutaneous Administration of PuO_2 and the Effect of Chelation Therapy, in *Radiobiology of Plutonium*, B. J. Stover and W. S. S. Jee (Eds.), pp. 213-220, The J. W. Press, Department of Anatomy, University of Utah, Salt Lake City (1972).

Katz, J., and M. H. Weeks, Absorption of Plutonium from the Gastrointestinal Tract of Rats: Effect of Plutonium Concentration, Hanford Biology Research Annual Report HW-30437, pp. 106-108 (1954).

Langham, W. H., S. H. Basset, P. S. Harris, and R. E. Carter, Distribution and Excretion of Plutonium Administered Intrave-

nously to Man, Los Alamos Scientific Laboratory Report LA-1151 (1950).

Mahlum, D. D., and M. R. Sikov, Effect of Age on Absorption of Plutonium from the Gastrointestinal Tract of Rats, Battelle Pacific Northwest Laboratory Annual Report BNWL-480(Vol. 1) pp. 40-41 (1967).

Muntz, J. A., and E. S. Guzman-Barron, Combination of Plutonium with Plasma Proteins, Manhattan District Declassified Document MDDC-1268 (1947).

National Committee on Radiation Protection, *Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and Water for Occupational Exposure*, National Bureau of Standards Handbook 69, U. S. Government Printing Office, Washington (1959).

Nénot, J. C., R. Masse, M. Morin, and J. Lafuma, An Experimental Comparative Study of the Behavior of ^{237}Np, ^{238}Pu, ^{239}Pu, ^{241}Am, and ^{242}Cm in Bone, *Health Phys.*, 22: 657-665 (1972).

Painter, E., E. Russell, C. L. Prosser, M. N. Swift, W. Kisieleski, and G. Sacher, Clinical Physiology of Dogs Injected with Plutonium, Metallurgical Laboratory Report CH-3858 (June 1946); also AECD-2042.

Park, J. F., E. B. Howard, and W. J. Bair, Acute Toxicity of Inhaled $^{238}PuO_2$ in Beagles, Battelle Pacific Northwest Laboratory Annual Report BNWL-1050(Vol. 1, Pt. 1), pp. 3.6-3.13 (1970).

Popplewell, D. S., and G. Boocock, Distribution of Some Actinides in Blood Serum Proteins, in *Diagnosis and Treatment of Deposited Radionuclides*, Proceedings of a Conference, Richland, Washington, 1967, H. A. Kornberg and W. D. Norwood (Eds.), pp. 45-55, Excerpta Medica Foundation, Amsterdam.

Russell, E. R., Plutonium Ingestion Studies, Biochemical Survey Section Monthly Report, Metallurgical Laboratory Report MUC-ERR-211 (June 1946).

Scott, K., H. Fisher, D. Axelrod, J. Crowley, A. J. Barber, and J. G. Hamilton, Metabolism of Plutonium in Rats, Metallurgical Laboratory Report CN-2383 (October 1944); also MDDC-1018, partially published in *J. Biol. Chem.*, 176: 283-293 (1948).

Smith, V. H., J. L. Palotay, H. A. Ragan, and B. J. McClanahan, Ingestion of Plutonium Oxide Particles by Swine, Battelle Pacific Northwest Laboratory Annual Report BNWL-280, pp. 40-43 (1966).

Stevens, W., F. W. Bruenger, D. R. Atherton, and B. J. Stover, Subcellular Distribution of ^{241}Am(III) and ^{239}Pu(IV) in Livers Studied Serially, University of Utah College of Medicine, Radiobiology Division, Annual Report COO-119-244, pp. 159-174 (1971).

Stover, B. J., D. R. Atherton, and N. Keller, Metabolism of ^{239}Pu in Adult Beagle Dogs, *Radiat. Res.*, 10: 130-147 (1959).

___, F. W. Bruenger, and W. Stevens, The Reaction of Pu(IV) with the Iron Transport System in Human Serum, *Radiat. Res.*, 33: 381-394 (1968).

Turner, G. A., and D. M. Taylor, The Transport of Plutonium, Americium, and Curium in the Blood of Rats, *Phys. Med. Biol.*, 13: 535-546 (1968).

Vaughan, J., B. Bleaney, and D. M. Taylor, Distribution, Excretion, and Effects of Plutonium as a Bone-Seeker, in *Handbook of Experimental Pharmacology*, Vol. 36, Uranium. Plutonium. Transplutonic Elements, H. C. Hodge, J. N. Stannard, and J. B. Hursh (Eds.), pp. 349-502, Springer-Verlag, Berlin (1973).

Weeks, M. H., J. Katz, W. D. Oakley, J. E. Ballou, L. A. George, L. K. Bustad, R. C. Thompson, and H. A. Kornberg, Further Studies on the Gastrointestinal Absorption of Plutonium, *Radiat. Res.*, 4: 339-347 (1956).