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Radiobiology of Plutonium

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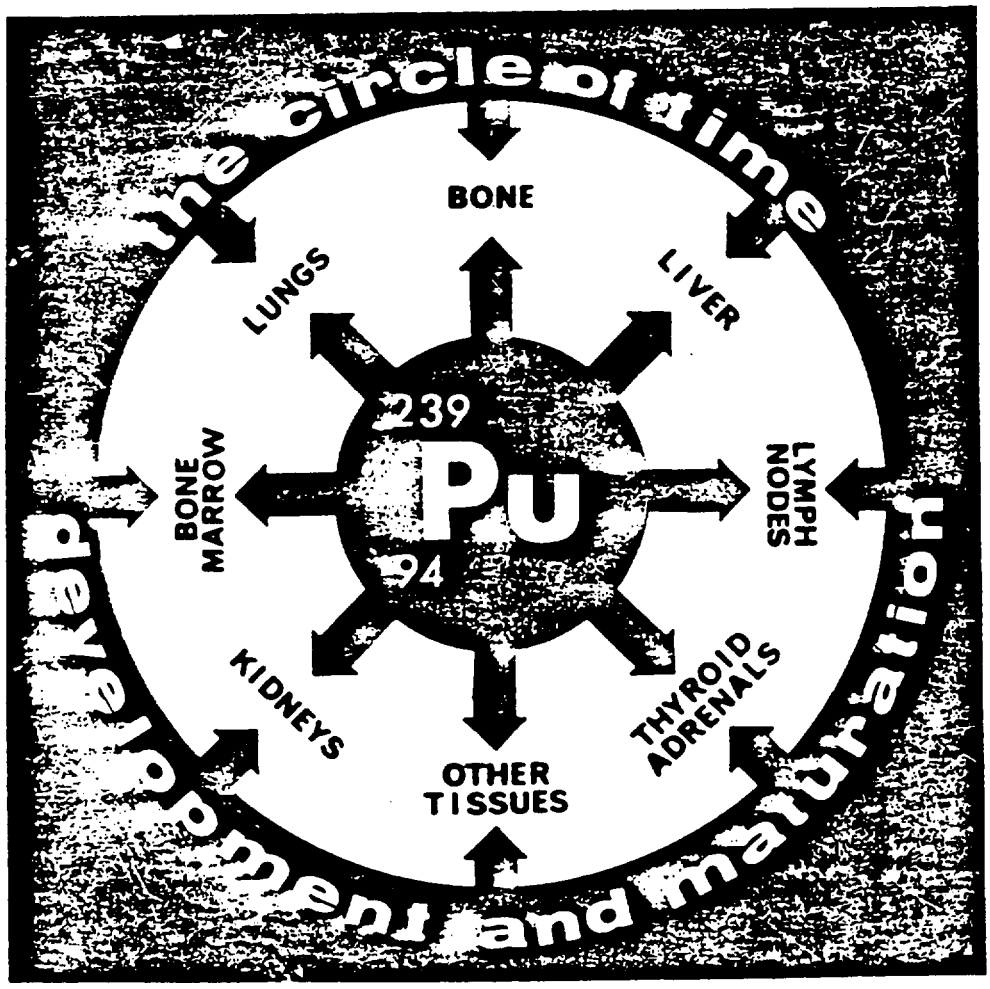

The Competitors..... Time and Irradiation

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Radiobiology of Plutonium

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:MENTS

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Patricia W. Durbin *

PLUTONIUM IN MAN: A NEW LOOK AT THE OLD DATA

ABSTRACT: *In order to determine the relationships between urinary Pu excretion and body Pu content, 18 persons (15 over the age of 45) were injected in 1945 and 1946 with tracer doses of ^{239}Pu. The original data have been critically reviewed and re-analyzed.*

A few days after injection, human soft tissues (other than blood and liver) contained as much as 20% of the Pu dose. Five to 15 months after injection the average liver Pu content was 31% of the dose for three cases with presumably normal liver function. Four to 457 days after injection mean total skeletal Pu was 49% for the seven cases judged to have most nearly normal livers and skeletons.

Pu is transported in blood combined with transferrin, the iron-transport protein, and is stored in the liver in association with stored iron. After being bound to transferrin, Pu partially traces the behavior of the carrier protein. The early phases of Pu transport which are apparently associated with extra-cellular fluid mixing, were prolonged in individuals with impaired circulation.

Maximum urinary Pu excretion occurred before the bulk of Pu was protein-bound. Minimum urinary excretion coincided with the time of maximum Pu-transferrin binding. These observations were taken to mean that some Pu is filtered by the kidney in the form of a low-molecular-

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weight chelate. Urinary Pu excretion was reduced by one-half in those persons who were anemic, presumably because of their more efficient Pu-transferrin binding.

Fecal excretion of Pu apparently represents secretion in bile and other digestive juices. Fecal excretion was reduced by one-half or more in those persons whose gastrointestinal tracts were judged not to be normally stimulated.

Semilogarithmic curves of Pu disappearance from plasma and of daily Pu excretion were prepared for each individual. "Normal" human Pu plasma and excretion equations (sums of exponentials) were constructed from the mean half-times and intercepts for the individual cases. All cases were included in the mean half-times — rates were apparently not affected by the individuals' various illnesses. Only the intercepts for those persons for whom a particular function was judged to be within normal limits were included in the mean intercepts.

Daily Pu excretion rates and total cumulative Pu excretion predicted from exponential equations were somewhat greater than predicted from the power functions of Langham et al., chiefly because only data from normally functioning excretory systems were included in the coefficients, but also because the fecal excretion assumed in the exponential model is higher than in other models.

Turnover of Pu in bone and soft tissues, storage of Pu in liver of the dog and pig, and storage of iron in man were reviewed. At tracer levels net loss of Pu from soft tissues and bone exceeds whole-body Pu loss, indicating continuous accumulation of Pu in the liver. Average soft-tissue release half-time was estimated to be not less than 480 days, and bone surface turnover for the whole adult human skeleton was estimated to be about 5% per year. For an individual on a diet adequate in iron and with normal iron stores, this model predicts that bone and liver will contain equal amounts of Pu 15 years after exposure.

INTRODUCTION

Plutonium was recognized as potentially dangerous even when the total amount of Pu in existence was only a few milligrams.[1] If the Metallurgical Laboratory efforts were successful, enormous amounts of plutonium — hundreds of times the world supply of radium — would be produced. The urgent need for biological studies of Pu was appreciated, and these were begun as soon as Pu could be spared from essential chemical investigations. On November 4, 1943, A. H. Compton[2] an-

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nounced to the Metallurgical Laboratory Project Council that the Clinton pile had "taken off." By January 19, 1944, 0.5 g of Pu had been separated,[3] and three weeks later, on February 8, 1944, Hamilton's group at Berkeley received 11 mg to begin tracer studies in rats.[4]

Pu contamination of Metallurgical Laboratory installations and personnel was a chronic problem,[5, 6] and one of the Health Division's pressing tasks was to devise a method of determining whether a Pu burden had been acquired. The first approach was analysis of Pu in urine,[7–9] and tracer data from rodents* were used to relate Pu in urine to the body burden. If urinalysis was to be a reliable assay for Pu, characterization of its behavior in man was essential. For this reason, 18 hospitalized persons were injected with tracer amounts of Pu in 1945 and 1946.[18]

The power-function curves of human Pu excretion constructed by Langham et al.[19, 20] used data from both the hospital patients and from several occupationally exposed persons, and provided a method of predicting Pu body content based on urinalysis. Langham's method has been reanalyzed many times.[21–23] There have been mathematical refinements, and analytical chemical and α-particle detection techniques have been improved,[24, 25] but the underlying assumptions are unchanged.

It seemed appropriate that this anniversary volume include a reexamination of the original data, gathered nearly 25 years ago, because meager as they are, they represent nearly all our human Pu experience. Study of the behavior of Pu in each patient might reveal differences in Pu metabolism (as a result of their various illnesses) that could be used to predict the behavior of Pu in healthy persons.

A retrospective study has the advantage of being able to draw on newer knowledge. Long-term excretion data are now available from the lower-dose dogs in the Utah experiment.[25, 29] The protein that binds Pu in plasma has been identified as transferrin, the iron-transport protein.[30–33] The kinetics of iron, the element normally carried by transferrin, have been worked out in detail.[34–37] Now, there is also some information on the behavior of Pu in two other large animals, the sheep[38, 39] and the pig.[40–43]

* The rodent tracer studies and inhalation experiments (Hamilton et al.[10, 11]) and attempts at Pu decontamination (Copp et al.[12]) by the Berkeley group, and the tracer and toxicity and inhalation studies in several species by Cole's group in Chicago (Finkle et al.,[13] Painter et al.,[14] Brues et al.,[15] Bloom[16] and Abrams et al.[17]) are the foundation of our knowledge of the biological behavior of Pu. Photocopies of the unpublished Metallurgical Laboratory reports are available at cost from the Division of Technical Information, P. O. Box 62, Oak Ridge, Tennessee, 37830.

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MATERIALS AND METHODS

The following brief description of the original data sources is included to eliminate confusion about the Berkeley and Chicago cases for which fragmentary reports have appeared more than once. Summaries of the histories of the published cases and histories of two previously unpublished cases are also included in Appendix 1.

Langham et al.[19] Cases HP-1 through HP-12 are described, including medical histories, injection data, hematologic data, blood chemistry, and Pu analyses of blood, urine, feces, and tissue specimens. Pu analyses of urine, feces (fecal data from Cal-1 were not included), and tissue specimens are reported for Cal-1, Chi-1, Chi-2, and Chi-3. Pu urinalyses are reported for three occupationally exposed persons. Pu radiochemical methods are reported in detail elsewhere.[44–46]

Russell and Nickson[14, 47, 48] All the original data from Chi-1 and Chi-2 are contained in Ref. 47, which includes case histories, injection data, hematologic examinations, and Pu analyses of urine, feces, and tissue specimens. Ref. 48 contains the original data for Chi-3 and fragmentary data from the other two cases. (Additional information was obtained from E. R. Russell for Chi-3.) Pu radiochemical techniques can be found in Refs. 49-51.

Crowley et al.[52] Most of the information obtained from Cal-1 is included in this report, which includes a brief medical history, injection data, and Pu analyses of urine, feces, blood, and biopsy specimens. Radiochemical techniques are also included. Additional information was obtained from raw data sheets, hospital records, and death certificates.

Foreman et al.[53] This report contains all the information from a case of occupational Pu exposure (designated herein as LASL-1).* Included are Pu exposure history and Pu analyses of urine and autopsy specimens. Radiochemical techniques are described elsewhere.[26]

Data from the laboratory animals were obtained from published curves and tables: dog,[28, 29, 54–56] sheep,[35, 39] swine[40–43] and rat.[10, 57, 58] B. J. Stover and D. R. Atherton kindly supplied original data for Pu excretion of individual dogs.

RESULTS

Plutonium in soft tissues

Organ and tissue weights were estimated from the recorded body

* Now designated as LASL-1-038 by the Los Alamos Scientific Laboratory.

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weight and the weight proportions of "Standard Man."[59, 60] The analytical results and calculated weights of tissues and organs and their total calculated Pu contents are shown in *Table I*.

The calculated Pu content of the soft tissues* of the six human beings is considerably greater than the 3% reported present in soft tissues of the beagle 22 days after intravenous injection.[23] It was possible to calculate from the data of Smith et al.[42] that the soft tissues of yearling miniature swine contained as much as 25% of the injected dose 6 days after intravenous injection of Pu(IV) citrate.

The movement of Pu out of the soft tissues of the six human cases is shown in *Figure 1*. Extrapolation of the initial steep portion of the curve indicates that about 24% of the injected Pu was present in these tissues (and their contained blood and extracellular fluid) 24 hours after injection. The equation of the exponential curve in *Figure 1* is

$$\text{Soft-tissue Pu} = 8\%e^{-0.096t} + 16\%e^{-0.00141t}, \qquad (1)$$

where t is days. The initial rate of Pu loss from the soft tissues of the high-dose dogs studied by Painter et al.[24] and from rats[10, 57] appears to be about the same as estimated for man. There is some indirect evidence from the Utah dogs that Pu continued to be deposited in liver and bone during the first few days after injection. Thus, the amount of Pu initially in the soft tissues of the dog (at least 20% can be accounted for in blood alone) was substantially more than the 3% measured at 22 days.[23] Most of the Pu that leaves the soft tissues of either dog or man does not leave the body, but is redistributed to the liver and skeleton. It appears that most of the Pu originally in the soft tissues of the dog is sufficiently labile to participate in this redistribution, but that nearly two-thirds of the Pu initially found in the soft tissues of man is more firmly bound.

Plutonium in the skeleton

The initial Pu content of the entire human skeleton was originally calculated by multiplying the mean Pu concentration of all the bone samples by 10 kg, the estimated average bone mass of "Standard Man",[59] yielding a calculated total skeletal Pu of 65%.

Since 1951, when the human Pu cases were reported, Pu has been measured in all the individual bones of the dog,[56] and in several bones of

* Unless otherwise specified, soft tissue includes muscle, skin, connective, lymphatic, and nervous tissue, fat, glands, all organs except liver, blood and other body fluids except bladder urine, and gastrointestinal contents. Thus the whole body consists of liver, bone and soft tissue.

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the rat,[42] rabbit,[68] and pig.[43] The results are all the same: vertebrae, ribs, and sternum — the bones sampled in the human cases — have higher initial Pu concentrations than the skeleton as a whole, which means that the total skeletal content of the human Pu cases was probably overestimated.

One method of estimating skeletal Pu uses the material balance,

$$Pu_{sk} = 100\% - (Pu_l + Pu_{st} + Pu_e), \qquad (2)$$

where Pu_{sk}, P_l, Pu_{st}, and Pu_e are the percent of injected dose in the skeleton, liver, soft tissues, and excreta, respectively. The maximum Pu_{sk} — that is, the amount of Pu left over after accounting for Pu_l, Pu_{st}, and Pu_e of each individual human Pu case — appears in the bottom row of *Table I*.*

The mean Pu_{sk} for all six cases, regardless of their health status, was 55% — 10% less than was originally calculated. Some of the reasons for this change are that the following have now been accounted for: (a) excretion between the end of collections and death; (b) Pu in all soft tissues whether sampled or not; and (c) Pu remaining in the circulation of the two cases from whom tissue samples were obtained 4 to 5 days after injection.

The livers of two cases were not normal. The liver of Chi-2 had been almost completely replaced by tumor. When HP-11 was injected, he was dying of hepatic failure (cirrhosis resulting from chronic alcoholism and malnutrition). If only the three cases with presumably normal livers are considered, the mean Pu_l is 31.2%, and the mean Pu_{sk} is 47% — nearly 18% less than originally estimated.[19]

Total skeletal Pu_{sk} can also be estimated from (a) the concentration in individual bones, (b) the ponderal (weight) relationships between individual bones and the whole skeleton, and (c) the distributional relationships between a radionuclide in individual bones and in the entire skeleton according to the equation

$$Pu_{sk} = \frac{BW \times fsk \times fb_i \times (Pu_i)}{fr_i}, \qquad (3)$$

where BW is the body weight in grams, fsk is the fraction of the body weight contributed by the skeleton, fb_i is the fraction of the skeletal

* Pu_l was not measured for Cal-1, so the range of Pu_{sk} shown for him uses as limits the highest and lowest measured values of Pu_l from three other cases that were considered to have approximately normal livers.

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Table I. (Part 1) Material balances of soft tissue and excreta. Six persons injected i.v. with Pu(IV) citrate, Pu(VI) nitrate, or Pu(VI) citrate.

	Pu(IV) Citrate								
	HP-5: 151 days p.i. *Male, 56 yr.* *70.8 kg*[a]			*HP-9: 456 days p.i.* *Male, 66 yr.* *63 kg*			*HP-11: 5 days p.i.* *Male, 68 yr.* *70.8 kg*[a]		
Soft Tissues	*%Pu/g*	*wt (g)*	*Calc. (%) dose*	*%Pu/g*	*wt (g)*	*Calc. (%) dose*	*%Pu/g*	*wt (g)*	*Calc. (%) dose*
Liver	0.032	1,340[b]	42.8	0.0144	1,600[b]	23.0	0.0053	2,325	12.3
Spleen	0.0007	184	0.13	0.0015	162	0.24	0.0048	184	0.89
Kidney	0.0002	312	0.062	0.0002	277	0.055	0.0015	312	0.47
Lung	0.0005	1,000	0.50				0.0016	1,000	1.60
Pancreas	0.0002	100	0.02	0.0002	90	0.018			
Intestines	0.00015	1,020	0.15				0.00045	1,020	0.46
Testes	0.0003	64	0.018				0.0012	64	0.077
Thyroid	0.0001	16	0.0016				0.0009	16	0.014
Adrenals	0.0004	14	0.0056				0.0022	14	0.031
Muscle	0.0002[c]	28,400	6.67	0.0002[c]	25,200	5.92	0.0002	28,400	5.68
Skin		4,950			4,410		0.0002	4,950	0.99
Residual soft tissue	0.0001[d]	23,080	2.31	0.0001[d]	22,280	2.23	0.0001[d]	22,200	2.22
Excreted[e]			5.20			16.5			2.00
Total (accounted for)			57.9			48.0			34.7
Skeleton (calc.)		10,300	42.1		9,166	52.0		10,300	65.3

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Table I. (Part 2) Material balances of soft tissues and excreta. Six persons injected i.v. with Pu(IV) citrate, Pu(VI) nitrate, or Pu(VI) citrate.

	Pu(VI) Citrate						*Pu(VI) Nitrate*		
	Chi-1: 160 days p.i. Male, 68 yr. 76.4 kg			*Chi-2: 17 days p.i. Female, 55 yr. 38.6 kg*			*Cal-1: 4 days p.i. Male, 58 yr. 58 kg*		
	%Pu/g[a]	*wt (g)*	*Calc. (%) dose*	*%Pu/g*[a]	*wt (g)*	*Calc. (%) dose*	*%Pu/g*[a]	*wt (g)*	*Calc. (%) dose*
Liver	0.0135	2,050[b]	27.8	0.0024	1,110	2.70		1,508	
Spleen	0.0025	260[b]	0.65	0.0012	85[b]	0.10	0.0019	167[b]	0.32
Kidney	0.00038	340[b]	0.12	0.0054	190[b]	1.03			
Lung	0.00058	1,950[b]	1.13	0.0016	490[b]	0.78			
Pancreas				0.0022	60[b]	0.13			
Intestines				0.00065	555	0.36			
Testes	0.00052	66	0.034						
Thyroid				0.0034	14	0.048			
Adrenals									
Muscle	0.00025[c]	30,560	8.98	0.0006	11,310	6.79	0.0004[c]	23,200	9.28
Skin		5,348		0.0006[c]	2,320	1.39	0.00058	4,550	2.64
Heart	0.00028	382	0.11	0.00105	250	0.26			
Diaphragm	0.00023								
Lung tumor	0.0017	32	0.054						

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Muscle	0.00025[c]	30,560	8.98	0.0[illegible]	11,310	6.79	0.0004[c]	23,200	9.28
Skin		5,348		0.00[illegible]	2,320	1.39	0.00058	4,550	2.64
Heart	0.00028	382	0.11	0.00105	250	0.26			
Diaphragm	0.00023								
Lung tumor	0.0017	32	0.054						
Lymph node	0.0015	764	1.16	0.00074	390	0.29			
Ovaries				0.00004	10	0.009			
Omentum							0.0004		
Subcutaneous tissue							0.0004		
Scar tissue							0.0011		
Residual soft tissue	0.00012[d]	23,800	2.98	0.0003[d]	14,700	4.41	0.0002[d]	16,690	3.34[b]
Blood									5.66
Excreted[e]			6.74			0.70			1.19
Total (accounted for)			49.8			19.0			25.7
Skeleton (Calc.)		9,428	50.2		7,125[i]	81.0		9,428[i] (mid-range 42.5)	

[a] Body weight estimated to be the mean weight of six male cases whose body weights were recorded.

[b] Measured tissue weight.

[c] Pu concentrations in muscle and skin (when not measured) were estimated to be the average of other measured soft tissues such as heart, pancreas, etc.

[d] Pu concentration of residual soft tissue was estimated to be one-half the concentration in skin and muscle.

[e] Measured totals are used when available. Excretion between the cessation of collections and deaths of HP-5 and HP-9 was estimated from extrapolation of the last available measurements and the slopes of the U and F curves of persons followed for longer times. Excreta from HP-11 were estimated to be the mean for all the other Pu(IV) citrate-injected cases.

[f] Includes 7.95%, the average Pu content of blood of the two sickest persons (HP-4 and HP-10), from whom blood samples were obtained at this time.

[g] %/g of Pu recalculated from original data.

[h] Includes 3.25% estimated from the tissues of Chi-2 and HP-11.

[i] Chi-2 was emaciated; her skeleton was assumed to be the average reported by Mechanik[41] for slightly built females. Cal-1 had lost 15 lb during his illness; his skeletal weight was calculated from his body weight in good health, 64.8 kg.

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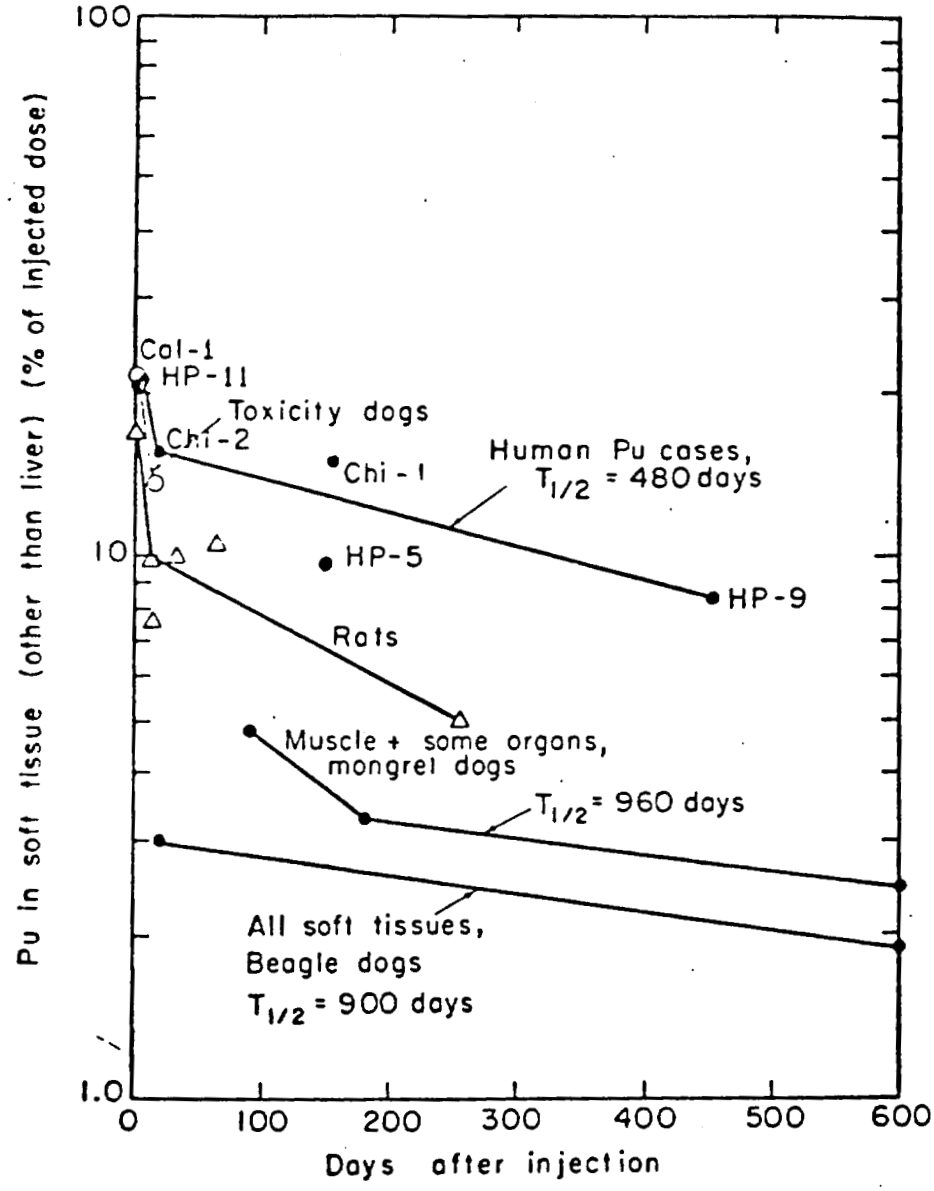

Fig. 1. Pu loss from soft tissue (other than liver) after intravenous injection of Pu(IV) citrate or Pu(VI) citrate. Rat data are from Scott et al.[10] and Carritt et al.[57]; toxicity dogs were those of Painter et al.[34]; mongrel dogs injected with $Pu(NO_3)_4$ were those of Rysina and Erokhin[54]; beagles were those of Stover et al.[28]

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weight contributed by the individual bone i (or a group of similar bones), (Pu_i) is the measured Pu concentration (%/g) in bone i, and fr_i is the fraction of the skeletal radionuclide contributed by bone i.

Bone specimens were obtained from nine cases. The analytical results are shown in *Table II*. The bone samples of the two Chicago cases and the three California cases had been subdivided into several parts, e.g., periosteum, marrow, spicules, cortex, etc. In order to make use of published whole-bone weights and intraskeletal radionuclide distributions, it was necessary to reconstruct whole-bone samples from the reported parts.[64]

The literature contains records of 29 complete dissections of fresh skeletons from weighed cadavers.[61, 65–70] The best estimates of fsk for the human skeleton are 14.6 ± 3%* and 11.9 ± 1.7% of the body weight for the adult male and female, respectively. The weights of the individual skeletons of the Pu cases were calculated and appear at the bottom of *Table I*. Marci and Borisov[71] dissected seven male and six female cadavers of persons who died in 1967. Groups of bones were weighed on modern equipment, and drying was avoided. Their dissections included only "careful preliminary removal of soft tissue", about what might be expected in the case of autopsy samples. The fb_i's derived from these data[71] were multiplied by the calculated weights of the skeletons of the Pu cases to obtain estimates of the wet weight of each sampled bone or group of bones.

Fractional distribution of Pu in the human skeleton introduces the greatest uncertainty into the ponderal calculation, because it has not been evaluated. Distribution of Pu in all the individual bones has been measured only in the dog.[56, 72] The use of the dog data to describe Pu distribution in the human skeleton has serious disadvantages. Differences in bone weight distribution, and presumably also the functional differences resulting from different patterns of weight bearing, are likely to be reflected in the radionuclide distributions in the skeletons of man and dog. The skeletal distribution of ^{241}Am has been determined in the dog,[73] and the results compare reasonably well with those for ^{239}Pu in the same species and with ^{241}Am in the monkey (P. W. Durbin, M. H. Williams, and N. Jeung, unpublished). At least one alkaline earth element has also been studied in each of these animals; ^{226}Ra in the dog skeleton,[72] and ^{90}Sr in the monkey skeleton.[74] Data were found from which it was possible to

* Mean ± standard deviation (S.D.).
S.D. = $[\Sigma(\text{dev})^2/(n-1)]^{1/2}$.

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Table II. Summary of Pu concentration in human bone samples (Pu_i) and calculation of total Pu in the sampled bones and total skeleton based on intraskeletal distribution of Ra and Sr in man, Am in monkey and Pu in dog.[a]

				% of Pu in total skeleton, based on[a]			
Case	*Bone sampled*	*(Pu_i) %/g*	*% of Pu (calc.)*	*Ra, Sr man*	*Am monkey*	*Pu dog*	*Material balance*
HP-5	Vertebra	0.0071	13.6	56	47	38	
	Rib (whole)	0.0070	4.47	36	76	38	
	Sternum	0.0050	0.72	40	48	40	
	Mean			44	57	38	42
HP-9	Vertebra	0.0080	13.6	56	47	39	
	Rib (whole)	0.0038	2.16	17[b]	37	18[b]	
	Mean			56	42	39	52
HP-11	Vertebra	0.0070	13.4	55	46	38	
	Rib (whole)	0.0068	4.34	35	74	37	
	Sternum	0.0096	1.38	77	92	77	
	Mean			56	71	51	65
HP12	Radius end	0.0187	2.36[c]		103		
	Patellae	0.0109	0.78[d]		162		
	Mean				132		
Chi-1	Rib[e]	0.0079	5.44	44	92	46	
	Sternum	0.0047	0.73	40	49	40	
	Mean			42	70	43	49
Chi-2	Rib[e]	0.0200	8.84	71	150	76	81
Cal-1	Rib[e]	0.0081	4.73	38	80	40	
Cal-2	Femur[e]	0.0436	12.5	>100			
Cal-3	Femur (cortex)[e]	0.0031	6.09	57			

[a] See text and Refs. 72-77.
[b] Omitted from average.
[c] Ends of radii and ulnae of adult rhesus monkeys contribute 33% of the whole-bone wet weight.
[d] Measurement of patellae separate from leg bones was made only for Sr in the monkey and represented 0.48% of the skeletal burden.
[e] Results published for subdivided samples. Whole bone reconstructed, see Ref. 64.

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calculate the distributions of ^{226}Ra and ^{90}Sr in the human skeleton.[73–77] (Details are published elsewhere.[64]) The estimates of the skeletal distributions of ^{226}Ra and ^{90}Sr in man agreed well. They also agreed generally (despite some specific species differences) with the distributions of ^{226}Ra and ^{90}Sr in the animals and qualitatively with the distributions of the actinide elements in the animals. The existence of a common intraskeletal distribution pattern among seemingly dissimilar elements is not too surprising, because the initial site of deposition of all the bone-seeking elements is on surfaces and initial deposition is related to vascularization and blood flow.[78]

Table II contains the solution of Equation (3) for each bone specimen, based on fr_i taken from alkaline earths in man, ^{241}Am in the monkey, or ^{239}Pu in the dog.* The Pu_{sk} of each human case calculated from Equation (3) is compared in *Table II* with the result obtained from the material balance. The best agreement between the two methods of calculating Pu_{sk} was achieved when fr_i was based on the alkaline earth distribution in man.

The calculated Pu_{sk} was greater than 100% for HP-12, an impossibility. The bone specimens from that case were fragments removed during surgical repair of comminuted fractures. Surgery occurred 21 days after the bones were fractured and 5 days after the Pu injection. Callus formation and resorption of damaged bone were probably well under way when the Pu was injected. Van Middlesworth[79] showed that Pu uptake in a healing fracture was about four times as great as in the contralateral normal bone when partial healing had been permitted to occur before Pu injection.

The small piece of femoral metaphysis from Cal-2 (designated as cortex) was evidently not normal. Even assuming uniform skeletal Pu deposition during rapid growth, the Pu_{sk} calculated from this sample also exceeded 100%. Although not stated, the biopsy specimen may have been taken from the distal femoral metaphysis, the site of a pathological fracture three months earlier.

If these two cases are excluded, the mean skeletal Pu of the remaining six cases is 49 ± 8.3%.

Plutonium in blood after intravenous injection

Serial blood samples were drawn at irregular intervals from 11 of

* The sources of error in total skeletal isotope calculated from Eq. (3) have been examined for an ideal case.[64]

ne samples Pu
otal skeleton based
in monkey and Pu

Pu in total in, based on*		
n key	Pu dog	Material balance
7	38	
6	38	
8	40	
7	38	42
7	39	
7	18[b]	
2	39	52
	38	
•	37	
2	77	
1	51	65
3		
2		
2		
2	46	
9	40	
0	43	49
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0	40	

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the Pu-injected individuals.[19] The first sample was taken 4 hours after injection in all but one case, Chi-1.[13] The longest post-injection time at which a reliable blood sample was obtained was 46 days. A semilogarithmic curve of Pu in the blood was prepared for each of the ten individuals from whom more than three blood samples were taken. Details of the construction of the blood curves appear elsewhere.[64]

Individual Pu blood curves are shown in *Figure 2* along with the curves for dog and sheep.* Case HP-2 was typical of the curves of most of the cases. Case HP-4 was the most unusual — rapid components were missing, and Pu remained in the blood for a much longer time. The blood curve of HP-7 is shown to demonstrate the leveling trend after the fifteenth day.

In spite of the variety of their illnesses, the blood curves of these individuals revealed a common pattern. As it moves out of the circulation, Pu is evidently tracing fundamental processes that are little disturbed by the specific pathological conditions. There was an equally remarkable similarity among the different species. The individual intercepts and half-times of the components designed P_2, P_3, and P_4 (see *Table III*) were not normally distributed about their means, and it was necessary to seek some aspect of the chemical status of Pu or the physiological status of the patients (or both) that would account for these variations.

Pu(IV) has been shown to combine with proteins in the plasma of the rat,[30, 81] dog,[32, 33] and man [31] — in particular the iron-transport protein, transferrin. The properties of transferrin and its metabolism, and the transport of iron and its release into developing red cells have been recently reviewed by Katz.[35] Plasma clearance of pre-equilibrated ^{59}Fe-transferrin has an average half-time of 96 minutes.[34, 35] Once bound to transferrin, Pu(IV) appears to be released much more slowly than iron, and the mechanism of release remains to be elucidated. However, because such a large fraction of Pu(IV) introduced into the circulation in monomeric form is quickly bound to transferrin — 85% in 1 hour in the rat [81] and 96% by the seventh hour in the dog[33] — the working hypothesis was adopted that Pu bound to transferrin traces, at least in part, the metabolism of the carrier protein.

* The Pu blood curve for the dog was constructed for the data given in *Figures 1* and *2* of Stover et al.[28] Percent Pu per ml plasma was converted to % Pu in total blood volume by using the blood volume for the beagle.[80] Long-term data were obtained from *Table 1* in Stover et al.[29] Data for the sheep were read from *Figure 3* of McClellan et al.[30]

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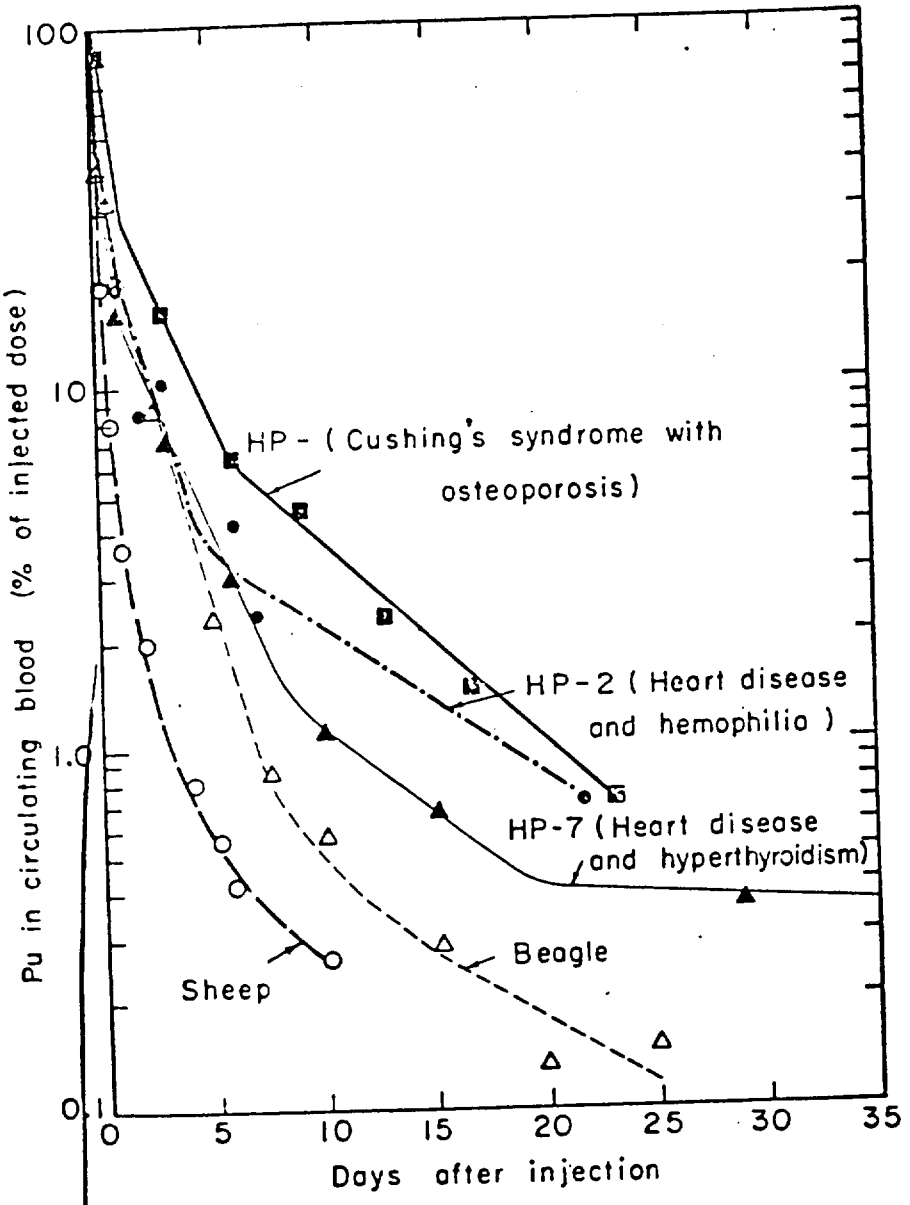

Fig. 2. Disappearance of Pu from the blood of man, dog, and sheep. Dog data are from Stover et al.[28], all dose levels combined; sheep data are from McClellan et al.[38, 39]

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The intercepts and the half-times of the unanalyzed individual Pu blood curves are shown in *Table III*. In the subsequent discussions of data presented as semilogarithmic plots, the slopes of the segments of the experimental curves are presented in terms of their half-times: half-time = $0.693/\lambda$, where λ is in units of time^{-1}. Half-times of raw curves are designated as S, and half-times of the exponential equations of these curves are designated as τ. Intercepts of raw curves are designated as A, and the coefficients of the exponential equations as α.

It can be inferred from the rapidity with which Pu initially leaves the circulation without appearing in significant amounts in the excreta or the major organs of deposition,[55] that some of the Pu not promptly bound to protein moves into the extracellular fluid. Half the body transferrin and the iron bound to it are extravascular.[35] The slow return of Pu to the circulation and its nearly complete protein binding after the first hour strongly suggest that some of the Pu that escapes into the extracellular fluid returns in bound form. The rates of movement of (a) unbound Pu out of the circulation and into the extracellular fluid, (b) Pu returning to the circulation bound to transferrin, and (c) Pu-transferrin into extracellular fluid[55] and excreta[22, 62] should all be influenced by the efficiency of the circulation.

Four persons were suffering from various heart and (or) circulatory ailments, all of which are associated with increased tissue fluid retention and decreased venous return. HP-3 was edematous, and her rate of tissue fluid movement was probably depressed. The parameters of the blood Pu curves of these five cases were compared with those of the remaining five cases, whose cardiovascular systems were apparently normal for their ages. The blood volumes of those patients with circulatory impairments lost Pu more slowly;* the half times of P_2 [PS_2 (normal) = 12.9 ± 3.6 hour, and PS_2 (impaired) = 19.1 ± 2.5 hour] were significantly different ($P = 0.01$).[83] Component P_3 was slower in the persons with poor circulation, but the difference was not significant. No effect of circulatory impairment on component P_4 was detected, suggesting that this and later components are only minimally influenced by circulatory status. Intercepts PA_2, PA_3, and PA_4 were higher when the circulation was not normal, but the scatter was so great that these differences were not significant.

* Although they could not be examined, the earliest components (combined here as P_1) were probably also slowed by circulatory impairment.

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Table III. Intercepts and half-times of *unanalyzed* semilogarithmic curves of Pu in human blood. Pu(IV) citrate injected intravenously.

Case	Day of last sample	PA_1 (%)	PS_1 (min)	PA_2 (%)	PS_2 (hr)	PA_3 (%)	PS_3 (days)	PA_4 (%)	PS_4 (days)	PA_5 (%)	PS_5 (days)	Circulation status[a]
HP-1	10	100[b]	50[b]	53	18	30	2.0					
2	22	100[b]	50[b]	55	16	26	1.6	5.6	7.4			Cardiac failure[c]
3	23	100[b]	50[b]	32	22.7	22	1.8	3.5	6.0			Edema[d]
4	23	—	—	100	18.5	44	2.2	13.0	5.5			Hypertension[e]
5	23	100[b]	50[b]	43	8.5	15	0.8	1.1	6.5			
6	22	100[b]	50[b]	46	11.5	22	1.0	2.4	4.5	0.29	95	
7	29	100[b]	50[b]	37	20	24	2.0	3.6	6.0	0.48		Cardiac failure[f]
8	42	100[b]	50[b]	45	14.5	22	1.7	4.3	6.0	0.24		
9	36	100[b]	50[b]	51	12	16	2.6	6.9	6.6	0.58		
10	30	100[b]	50[b]	60	18.5	33	2.3	4.8	6.8	0.49		Cardiac failure[g]
12	46	100[b]	50[b]							0.64	82	
Normal circulation,			No. cases	5	5	5	5	5	5	4	2	
Mean				47.6	12.9	21	1.62	3.7	5.9	0.44	88	
±S.D.				4.2	3.6	6.0	0.74	2.5	1.5	0.20	13	
Impaired circulation,			No. cases	5	5	5	5	4	4	2		
Mean				56.8	19.1	29.8	1.98	6.1	6.3	0.48		
±S.D.				26.9	2.5	9.0	0.29	4.0	0.8	0.01		

[a] Status of circulation obtained from case histories."
[b] Fitted to 100% at t = 0, and to 66% at t = 30 min.
[c] HP-2: "Essential hypertension with hypertensive cardiovascular disease and coronary insufficiency."
[d] HP-3: "Hepatitis with hypoproteinemia and dependent edema."
[e] HP-4: "Cushing's syndrome with hypertension, hypertensive heart disease."
[f] HP-7: "Rheumatic heart with mitral insufficiency and auricular fibrillation, hospitalized for cardiac decompensation."
[g] HP-10: "Acute congestive heart failure."

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A five-component exponential Pu blood curve was constructed by use of the mean intercepts and half-times of those individuals who were judged to be free of debilitating heart or vascular disease. Each mean component was plotted as a straight-line segment, and the equation of the composite curve was obtained by standard graphic methods. The parameters of the equations of the human blood curve are given in *Table IV* with those of the Pu plasma or blood curves of several other species.

Components P_1, P_2 and P_3 were affected by impairment of the circulation. Component P_1 (not well defined for man, half-times ranging from a few minutes to about 1 hour) seems to be associated with circulatory mixing, movement of unbound Pu into extracellular fluid, and uptake of Pu in bone and liver. Component P_2 (half-time 7 to 8 hours) seems to be related to the accumulation of Pu by bone. Iron metabolism suggests the mechanism leading to components P_3 and P_4. Component P_3 (half-time 1 to 2 days and not observed in the rat) may be related to the return of Pu-transferrin to the circulation from extracellular fluid. The last short-term component, P_4 (half-time 5 to 6 days) may be related to the destruction of the protein portion of the Pu-transferrin complex, or to a slower component of feedback from soft tissue.

The material balance of Pu in swine suggests loss of Pu from bone as an important source of plasma Pu after the first few days post injection. A long-term component, P_5, was found for the dog and pig (half-time about 230 days), and is probably related to feedback of Pu from short-lived bony structures and soft tissues. Only the dog has been observed for a long enough time to permit identification of a very slow component (half-time about 5500 days), which may be related to release of Pu from the liver as well as from slowly metabolizing portions of the skeleton.

Renal excretion of plutonium

The daily urinary excretion of each Pu-injected individual was given through the end of collections or through 138 days after Pu injection in *Table VI* of Langham et al.[19] Additional excretion data for Chi-1, Chi-3, and Cal-1 through 155, 163, and 341 days, respectively, were available in the original references.[47, 49f, 52] There is a great deal of scatter in the individual data; it could be caused by incomplete collection, analytical errors, or fluctuations in the physical condition of the patients.[24] The best straight-line segments were drawn on semilogarithmic plots of daily urinary excretion, and the resulting curves (shown in Appendix 2) were analyzed graphically.

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Table IV. Disappearance from circulating blood of intravenously injected Pu(IV) citrate. Parameters of equations[a] of experimental plasma (or whole blood) Pu curves of rat, dog, and sheep; and of constructed blood Pu curve for a human being with no circulation impairment.[b]

Species	*Day of last sample*	P_{α_1} *(%)*	P_{τ_1} *(min.)*	P_{α_2} *(%)*	P_{τ_2} *(hr)*	P_{α_3} *(%)*	P_{τ_3} *(days)*	P_{τ_4} *(%)*	P_{α_4} *(days)*	P_{α_5} *(%)*	P_{τ_5} *(days)*	*Reference*
Rat	8	60.3	58	37.3	8.2			0.8	6.0			89
Dog[c]	5	45	3-111	20.5	7.8	44	1.7					14
Dog	3,000	44	11-48	19.5	7.3	30	1.0	2.1	5.0	0.081	220[d]	28, 29
Sheep	10	68	24	25	2-5	5.8	1.6	1.1	4.9			39
Pig	475									0.50	230[e]	40
Man[a]	42	52.4	20	27.1	7.3	17.2	1.2	3.3	5.0	0.44	88	

[a] $P_t\ (\%) = \sum_{i=1}^{5} P_{\alpha i} \exp(-0.693t/P_{\tau i})$.

[b] See text and *Table III*.

[c] Pu(VI) citrate, 0.05 μCi/kg.

[d] An additional long-term component emerged at 800 days post injection. $P_{\alpha 6} = 0.045\%$, $P_{\tau 6} = 5500$ days[20].

[e] Average of two components: $P_{\alpha 6} = 0.41\%$, $P_{\tau 6} = 66$ d; $P_{\alpha 6} = 0.33\%$, $P_{\tau 6} = 380$ d.

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It is appropriate at this point to summarize what is known or can be inferred about the renal excretion of iron. Under normal physiological conditions only a tiny fraction of plasma iron exists in forms other than bound to transferrin. Urinary excretion of iron is only 0.1 mg to 0.2 mg daily equivalent to a urinary clearance of about 3% of plasma iron.[84] The normal mechanisms of urinary iron excretion probably include (a) filtration of low-molecular-weight chelates, (b) exfoliation of kidney, bladder, or urethra cells all of which contain small amounts of iron, and (c) leakage of transferrin-bound iron through the glomerulus or tubules. Another possible source of urinary iron may arise during transferrin catabolism in the kidney. The ability of the kidney to excrete unbound iron can be inferred from the observation that 1% to 2% of injected ^{59}Fe-ascorbate could be found in the earliest urine samples.[85]

The amount of Pu excreted in the urine at any time should depend at least in part upon the extent of Pu-transferrin binding (or binding to other proteins) and the filterability of low-molecular-weight Pu chelates. The rates of production and destruction of transferrin, hence, the amount of transferrin circulating[35] and the latent binding capacity (binding sites not already occupied by iron) are related to hematopoiesis and dietary iron intake.[36] Both the amount and latent binding capacity of transferrin are increased following acute hemorrhage and in iron-deficient anemia, and both are reduced in hemolytic anemias, acute hepatitis, and hemochromatosis.[35] The extent of Pu-transferrin binding and the rate of its release also appear to be related to and affected by the status of hematopoiesis.

Some individuals consistently excreted more Pu than others. In order to discover whether urinary Pu excretion could be related to physiological status, urinary Pu was summed for the earliest and latest 6-day intervals in which excreta were collected from all the patients. Medical histories were examined for information on renal function, hepatic protein synthetic capacity, and hematologic status.

The influence of anemia associated with an elevated latent iron binding capacity (reduced transferrin saturation) on urinary Pu excretion was clear. During the first 6 days post injection the four anemic Pu(IV)-injected patients excreted significantly less Pu in their urine (0.60% ± 0.15%) than did those whose hemograms were presumably normal (1.05 ± 0.25%.) Lower initial Pu excretion is what would be expected on the basis of the increased binding capacity of transferrin associated with most anemias.[36] During the interval of 19 to 24 days, the

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last 6 days for which excreta were collected from all the Pu(IV)-injected patients, the urinary Pu of the anemic patients (0.13% ± 0.06%) was slightly more than that of the hematologically normal patients (0.11% ± 0.03%), though not significantly so.

The urine curves of the four persons studied longest and the best curves that could be drawn for the dog and the pig are shown in *Figure 3*. The majority of the individual Pu urine curves contained two to four distinct segments, depending upon how long excreta were collected.

The means ± standard deviation of the raw intercepts and half-times were calculated (see *Table IV*) for the ten Pu(IV)-injected persons, six judged to have normal kidney and hematopoietic function, and four judged to be anemic. The intercepts of the first two components, UA_1 and UA_2, of the Pu urine curves of the presumably normal persons were almost twice as large as UA_1 and UA_2 determined for the anemic cases. UA_3 of the normal group was substantially lower than UA_3 of the anemic group. The half-times of these three components of the Pu urine curves were not affected by anemia or kidney disease. Although the amounts of Pu excreted in the urine were altered as a result of the various physiological processes associated with anemia, their rates were apparently unaffected.

The average intercept, UA_1, of the Pu(VI)-injected cases was greater, and the half-time, US_1, was less than the values of these parameters determined for either the normal or anemic Pu(IV)-injected group. The greater early urinary excretion of Pu(VI) citrate suggests that Pu in this form is more readily filtered by the kidney than is Pu(IV) citrate. The more rapid decay of the initial urinary component is in accord with Bruenger's suggestion[56] that Pu(VI) protein binding is more stable than that of Pu(IV). The average intercepts and half-times of U_2, U_3, and U_4 of the Pu(VI)-injected persons were either the same as, or not very different from, the values of these parameters determined for the group of Pu(IV)-injected cases with normal kidneys and normal hematopoiesis.

For radiological protection purposes the need is characterization of a Pu urine curve representative of an adult human being in reasonably good health. Therefore, in this analysis data were excluded from those persons judged to have obviously abnormal kidney function or abnormal plasma Pu binding (the anemic persons). A five-component exponential curve was constructed; the raw intercepts and half-times are shown in *Table V*, and the parameters of its equation appear in *Table VI*.

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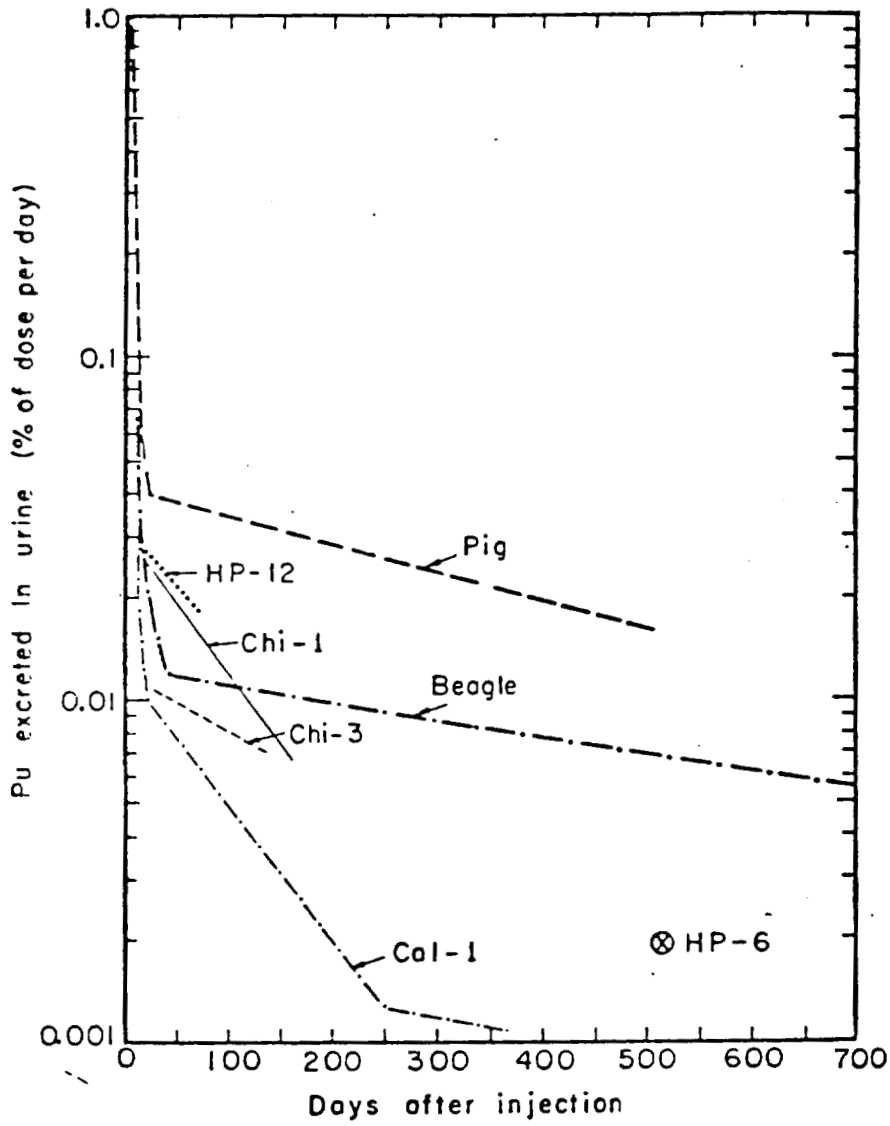

Fig. 3. Daily urinary Pu excretion by several Pu-injected persons, dogs and miniature swine. Swine data are from Clarke et al.[40]; dog data are from B. J. Stover and D. R. Atherton (original data) 0.1 μCi/kg groups only.

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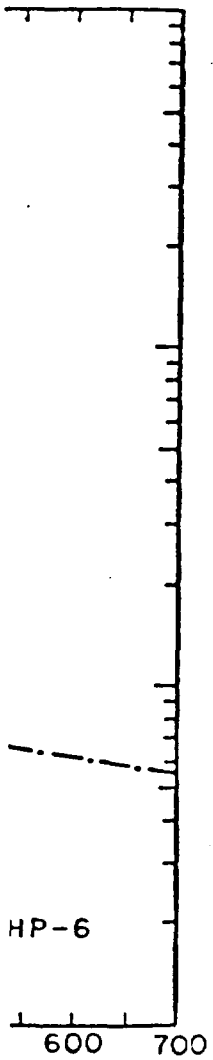

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only.

The half-times of the early components of the Pu urine curve were not noticeably affected by the physical disabilities of the individual patients, and the half-times of all the Pu(IV) urine curves were included in the calculated averages for each component. Pu(IV) is deemed most likely to be the chemical form of Pu encountered in an occupational exposure, and for this reason the Pu(VI)-injected cases were omitted from the calculated mean of US_1. The half-times of the later components of the urine curves of the Pu(VI)-injected individuals were not different from those determined for the persons given Pu(IV); therefore, all half-time determinations have been included in calculation of US_2, and US_3. Only Chi-3 and Cal-1, who were both injected with Pu(VI), provide any estimate of US_4, but neither was followed long enough to define it closely.

The only human Pu urine measurements at post-injection intervals sufficiently long to permit estimation of the slope of the next component, US_2, are two samples obtained from HP-6, 525 and 1610 days post injection. The line joining these two points has a half-time of 1250 days, only one-third the value of US_3 in the Pu urine curve of the dog. US_3 and US_4 were not defined for HP-6 because collections were terminated too soon, but if US_3 and US_4 for HP-6 are similar to the other cases, then the urine curve for HP-6 should bend between the two late sample points, and US_2 should be greater than 1250 days.

Some long-term urine data from four occupationally exposed persons are shown in *Figure 4*: WBG, DLW, and WAB, from whom urine specimens were obtained periodically for as long as 1698 days after termination of Pu exposure;[52] and LASL-1 who was followed for 3500 days after cessation of his initial high level Pu exposure.[53] The latter case is complicated because the individual returned to work with Pu, but at much lower levels, 2350 days after the end of his first Pu exposure period. The occupational data suggest that the longest half-time of the human Pu urine curve is perhaps as long as 13,400 days — the least-squares-fitted slope of the LASL-1 urinalysis data.* In the absence of reliable human data, and because of the half-times of comparable early portions of the human Pu urine curves are similar to those in the dog and pig, 4000 days (11 years) was selected as a working value for US_3 for man.

* The data points shown in *Figure 4* for LASL-1 are average of all the urinalyses taken during each 6-month interval: the original data appear in *Table 3* of Foreman et al.[53] These averages were not weighted for the number of analyses, and zero values were ignored.

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Table V. Intercepts and half-times of *unanalyzed* human urine Pu curves.

Case	Day of last sample	UA_1 %/day	US_1 days	UA_2 %/day	US_2 days	UA_3 %/day	US_3 days	UA_4 %/day	US_4 days	UA_5 %/day	US_5 days
Pu (IV) citrate											
Normal[a]											
HP-2	34	0.58	1.9	0.105	8.	0.0098[b]					
HP-3	23(1,610)[c]	0.76	1.1	0.270	2.8	0.0205[b]		0.0035[b]		0.0011[b]	
HP-5[d]	22	0.40	1.1	0.050	9.3	0.0240	71				
HP-6[d]	22(1,698)[c]	0.35	2.1	0.092	6.5	0.017[b]		0.0050[b]		0.0015[b]	1,250[b]
HP-8	65	0.46	1.2	0.148	5.1	0.023	64				
HP-10	30	0.55	1.9	0.162	5.						
Mean		0.54[e]	1.65	0.138	6.1	0.0189	68	0.00425		0.0013	
±S.D.		0.12	0.44	0.05	2.3	0.006					
Anemic											
HP-1	25	0.21	2.7	0.097	9.						
HP-7	37	0.28	2.6	0.044	9.	0.0100[b]					
HP-9	36	0.24	1.2	0.100	5.	0.0400	45				
HP-12	58		—	0.112	7.	0.0330	42				
Mean		0.24	2.1	0.088	7.6	0.0277	44				
±S.D.		0.03	0.58	0.03	1.6	0.005					

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P-1	25	0.21	2.7	0.097	9.				
HP-7	37	0.28	2.6	0.014	9.	0.0100			
HP-9	36	0.24	1.2	0.100	5.	0.0100	45		
HP-12	58		—	0.112	7.	0.0330	42		
Mean		0.24	2.1	0.088	7.6	0.0277	44		
±S.D.		0.03	0.58	0.03	1.6	0.015			
Abnormal kidney									
HP-4	26	0.50	1.9	0.200	7.				
Pu (VI) citrate or $PuO_2(NO_3)_2$									
Anemic									
Cal-1	341	0.60	1.0	0.180	4.6	0.012	71	0.0019	460
Chi-1[f]	155	2.53	0.33	0.220	3.6	0.035	67		
Chi-2[f]	15	0.27	1.4	0.058	8.0				
Mean		1.22	0.86	0.124	6.3	0.0223	60		
±S.D.		1.01	0.45	0.089	2.6	0.012			
No information									
Chi-3[g]	164	1.50	0.7	0.038	9.	0.020	42	0.011	440

[a] Renal function and erythropoiesis judged to be within normal limits.
[b] Estimated from constructed curves shown in Appendix 2abc. US_4 of HP-6 defined by two points at 525 and 1,610 days.[44]
[c] Single samples taken at these late post-injection intervals.[8]
[d] No published hematologic data, but presumed to be within normal limits.
[e] Underlined means were compared with the means immediately below by use of the t-test and "p" = 0.05.[53]
[f] Kidneys abnormal.
[g] Both renal and hematopoietic function can be impaired in the advanced stages of Hodgkin's disease. (Included in Pu(VI) group mean.)

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Table VI. Urinary and fecal excretion of Pu by adult man, young adult beagle, and adolescent miniature swine. Parameters of exponential excretory equations.[a]

	α_1 %/day	τ_1 days	α_2 %/day	τ_2 days	α_3 %/day	τ_3 days	α_4 %/day	τ_4 days	α_5 %/day	τ_5 days
Normal Man										
Urine[b]	0.41	1.2	0.12	5.5	0.013	42	0.003	300	(0.0012)[d]	(4,000)[d]
Feces[c]	0.60	2.0	0.16	6.6	0.012	56	(0.002)[d]	380	(0.0012)[d]	(4,000)[d]
Dog[e]										
Urine	4.6[f]	0.48[f]	0.15	3.3			0.008	450	0.004	3,850
Feces	3.0	2.3	0.31	4.6	0.08	14	0.007	350	0.0046	3,850
Swine[g]										
Urine	0.48	0.60	0.23	2.5	0.05	10	0.042	380		
Feces			0.37	1.5	0.18	10	0.012	325		

[a] U_t (%/day) or F_t (%/day) $= \sum_{n=i}^{n} \alpha_i \exp(-0.693t/\tau_i)$.

[b] Kidney function and hematopoiesis presumed to be within normal limits.

[c] Liver and digestive tract function pressumed to be within normal limits.

[d] Estimated.

[e] Stover et al.[20] and B. J. Stover and D. R. Atherton, original data; 0.1μCi/kg and 0.3μCi/kg groups only.

[f] Average of two components $U\alpha_{1a}$ = 4.1%/day, $U\tau_{1a}$ = 0.2 day; $U\alpha_{1b}$ = 1.9%/day, $U\tau_{1b}$ = 0.8 day.

[g] Data read from *Figure 1* of Clarke et al.[10]

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