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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.[21–25] There have been mathematical refinements, and analytical chemical and α-particle detection techniques have been improved,[26, 27] 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.[28, 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[18, 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,[38, 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.[28] 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

$$\text{Soft-tissue Pu} = 8\%e^{-0.096t} + 16\%e^{-0.0014t}, \qquad (1)$$

where t is days. The initial rate of Pu loss from the soft tissues of the high-dose dogs studied by Painter et al.[14] 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.[28] 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,[62] 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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