PLUTONIUM IN MAN:
A NEW LOOK AT THE OLD DATA
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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-
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. 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
announced to the Metallurgical Laboratory Project Council that the Clin-
ton pile had “taken off.” By January 19, 1944, 0.5 g of Pu had been
separated, 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 per-
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 rodents10 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 pre-
pdicting 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 im-
proved,26,27 but the underlying assumptions are unchanged.

It seemed appropriate that this anniversary volume include a re-
examination 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 sheep38,39 and the
pig.40-43

* The rodent tracer studies and inhalation experiments (Hamilton et al.16,17)
and attempts at Pu decontamination (Copp et al.19) by the Berkeley group,
and the tracer and toxicity and inhalation studies in several species by Cole's
group in Chicago (Finkle et al.,19 Painter et al.,19 Brues et al.,19 Bloom20 and
Abrams et al.19) 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 82,
Oak Ridge, Tennessee, 37830.
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 Nickson18 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.23 24 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.23 24 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.56

Data from the laboratory animals were obtained from published curves and tables: dog,28 29 54-56 sheep,38 39 swine40-43 and rat.10 37 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.
weight and the weight proportions of "Standard Man,"\textsuperscript{50,60} The analytical results and calculated weights of tissues and organs and their total calculated Pu contents are shown in Table 1.

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.\textsuperscript{28} It was possible to calculate from the data of Smith et al.,\textsuperscript{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

\[
\text{Soft-tissue Pu} = 8\%e^{-0.996t} + 16\%e^{-0.0014t},
\]

where \( t \) is days. The initial rate of Pu loss from the soft tissues of the high-dose dogs studied by Painter et al.,\textsuperscript{14} and from rats\textsuperscript{16,67} 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.\textsuperscript{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.

\textit{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,"\textsuperscript{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,\textsuperscript{24} 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.
the rat, rabbit, and pig. 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,

$$\text{Pu}_{sk} = 100\% - (\text{Pu}_1 + \text{Pu}_{st} + \text{Pu}_e),$$

where Pu$_{sk}$, Pu$_1$, 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$_1$, 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$_1$ is 31.2%, and the mean Pu$_{sk}$ is 47%—nearly 18% less than originally estimated.

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

$$\text{Pu}_{sk} = \frac{\text{BW} \times f_{sk} \times f_{bi} \times (\text{Pu}_1)}{f_{ri}},$$

where BW is the body weight in grams, f$_{sk}$ is the fraction of the body weight contributed by the skeleton, f$_{bi}$ is the fraction of the skeletal

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* Pu$_1$ 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$_1$ from three other cases that were considered to have approximately normal livers.
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.

<table>
<thead>
<tr>
<th>Soft Tissues</th>
<th>%Pu/g</th>
<th>wt (g)</th>
<th>Calc. dose (%)</th>
<th>%Pu/g</th>
<th>wt (g)</th>
<th>Calc. dose (%)</th>
<th>%Pu/g</th>
<th>wt (g)</th>
<th>Calc. dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.032</td>
<td>1,340^b</td>
<td>42.8</td>
<td>0.0144</td>
<td>1,600^b</td>
<td>23.0</td>
<td>0.0053</td>
<td>2,325</td>
<td>12.3</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.0007</td>
<td>184</td>
<td>0.13</td>
<td>0.0015</td>
<td>162</td>
<td>0.24</td>
<td>0.0048</td>
<td>184</td>
<td>0.89</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.0002</td>
<td>312</td>
<td>0.062</td>
<td>0.0002</td>
<td>277</td>
<td>0.055</td>
<td>0.0015</td>
<td>312</td>
<td>0.47</td>
</tr>
<tr>
<td>Lung</td>
<td>0.0005</td>
<td>1,000</td>
<td>0.50</td>
<td>0.0002</td>
<td>90</td>
<td>0.018</td>
<td>0.0016</td>
<td>1,000</td>
<td>1.60</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.0002</td>
<td>100</td>
<td>0.02</td>
<td>0.0002</td>
<td>90</td>
<td>0.018</td>
<td>0.00045</td>
<td>1,020</td>
<td>0.46</td>
</tr>
<tr>
<td>Intestines</td>
<td>0.00015</td>
<td>1,020</td>
<td>0.15</td>
<td>0.0003</td>
<td>64</td>
<td>0.018</td>
<td>0.0009</td>
<td>16</td>
<td>0.014</td>
</tr>
<tr>
<td>Testes</td>
<td>0.0003</td>
<td>64</td>
<td>0.018</td>
<td>0.0009</td>
<td>16</td>
<td>0.014</td>
<td>0.0002</td>
<td>14</td>
<td>0.031</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.0001</td>
<td>16</td>
<td>0.0016</td>
<td>0.0002</td>
<td>14</td>
<td>0.031</td>
<td>0.0002</td>
<td>28,400</td>
<td>5.68</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.00004</td>
<td>14</td>
<td>0.0056</td>
<td>4,410</td>
<td>0.0002</td>
<td>4,950</td>
<td>0.0002</td>
<td>28,400</td>
<td>5.68</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.0002^c</td>
<td>28,400</td>
<td>6.67</td>
<td>0.0002^c</td>
<td>25,200</td>
<td>5.92</td>
<td>0.0002</td>
<td>28,400</td>
<td>5.68</td>
</tr>
<tr>
<td>Skin</td>
<td>4,950</td>
<td></td>
<td></td>
<td>4,950</td>
<td>0.0002</td>
<td>4,950</td>
<td>0.0002</td>
<td>4,950</td>
<td>0.99</td>
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<tr>
<td>Residual soft tissue</td>
<td>0.0001^d</td>
<td>23,080</td>
<td>2.31</td>
<td>0.0001^d</td>
<td>22,280</td>
<td>2.23</td>
<td>0.0001^d</td>
<td>22,200</td>
<td>2.22</td>
</tr>
<tr>
<td>Excreted^e</td>
<td></td>
<td>5.20</td>
<td>16.5</td>
<td></td>
<td>48.0</td>
<td>34.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (accounted for)</td>
<td></td>
<td>57.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeleton (calc.)</td>
<td>10,300</td>
<td>42.1</td>
<td></td>
<td>9,166</td>
<td>52.0</td>
<td></td>
<td>10,300</td>
<td>65.3</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)NMF, \(^b\)NED, \(^c\)NDF, \(^d\)NT, \(^e\)number of excreta
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.

<table>
<thead>
<tr>
<th></th>
<th>Pu(VI) Citrate</th>
<th>Pu(VI) Nitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi-1: 160 days p.i.</td>
<td>Cal-1: 4 days p.i.</td>
</tr>
<tr>
<td></td>
<td>Male, 68 yr.</td>
<td>Female, 55 yr.</td>
</tr>
<tr>
<td></td>
<td>76.4 kg</td>
<td>38.6 kg</td>
</tr>
<tr>
<td>Liver</td>
<td>0.0135</td>
<td>2,050&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.0025</td>
<td>260&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.00038</td>
<td>340&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lung</td>
<td>0.00058</td>
<td>1,950&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.0022</td>
<td>60&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intestines</td>
<td>0.00052</td>
<td>66</td>
</tr>
<tr>
<td>Testes</td>
<td>0.00052</td>
<td>66</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.0025&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30,560</td>
</tr>
<tr>
<td>Adrenals</td>
<td>5,348</td>
<td>2,320</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.00028</td>
<td>382</td>
</tr>
<tr>
<td>Skin</td>
<td>0.00023</td>
<td>32</td>
</tr>
<tr>
<td>Heart</td>
<td>0.00028</td>
<td>382</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>0.00023</td>
<td>32</td>
</tr>
<tr>
<td>Lung tumor</td>
<td>0.00028</td>
<td>382</td>
</tr>
<tr>
<td>Tissue Type</td>
<td>Activity (Bq)</td>
<td>Concentration (Bq/g)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Lymph node</td>
<td>0.0015</td>
<td>1.16</td>
</tr>
<tr>
<td>Ovaries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omentum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scar tissue</td>
<td>0.00012†</td>
<td>2.98</td>
</tr>
<tr>
<td>Residual soft tissue</td>
<td>0.00034</td>
<td>0.70</td>
</tr>
<tr>
<td>Blood</td>
<td>0.00024</td>
<td>6.74</td>
</tr>
<tr>
<td>Excreted</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Total (accounted for)</td>
<td>49.8</td>
<td>19.0</td>
</tr>
<tr>
<td>Skeleton (Calc.)</td>
<td>9,428</td>
<td>50.2</td>
</tr>
</tbody>
</table>

* Body weight estimated to be the mean weight of six male cases whose body weights were recorded.
* Measured tissue weight.
* Measured total was 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.
* 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.
* Includes 3.25% estimated from the tissues of Chi-2 and HP-11.
* Chi-2 was emaciated; her skeleton was assumed to be the average reported by Mechanik for slightly built females. Cal-1 had lost 15 lbs during his illness; his skeletal weight was calculated from his body weight in good health, 64.8 kg.
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.\textsuperscript{10} and Carritt et al.\textsuperscript{37}; toxicity dogs were those of Painter et al.\textsuperscript{14}; mongrel dogs injected with Pu(NO\textsubscript{3})\textsubscript{4} were those of Rysina and Erokhin\textsuperscript{44}; beagles were those of Stover et al.\textsuperscript{28}

\textbf{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.\textsuperscript{10} and Carritt et al.\textsuperscript{37}; toxicity dogs were those of Painter et al.\textsuperscript{14}; mongrel dogs injected with Pu(NO\textsubscript{3})\textsubscript{4} were those of Rysina and Erokhin\textsuperscript{44}; beagles were those of Stover et al.\textsuperscript{28}
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 $f_{ri}$ 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 $f_{sk}$ for the
human skeleton are $14.6 \pm 3\%$ and $11.9 \pm 1.7\%$ 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. Marei and Borisov73 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 ex-
pected in the case of autopsy samples. The $f_{bi}$’s derived from these data71
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 mea-
sured only in the dog.66, 72 The use of the dog data to describe Pu distri-
bution 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,78 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 $^{89}$Sr
in the monkey skeleton.74 Data were found from which it was possible to

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* Mean \pm standard deviation (S.D.).
S.D. = \[ \sqrt{\frac{\sum (\text{dev})^2}{n-1}} \]
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.*

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

^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.
I calculate the distributions of $^{226}$Ra and $^{90}$Sr in the human skeleton. 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.

Table II contains the solution of Equation (3) for each bone specimen, based on $f_1$ taken from alkaline earths in man, $^{241}$Am in the monkey, or $^{239}$Pu in the dog.* The $P_{sk}$ 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 $P_{sk}$ was achieved when $f_1$ was based on the alkaline earth distribution in man.

The calculated $P_{sk}$ 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 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 $P_{sk}$ 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.

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the Pu-injected individuals. The first sample was taken 4 hours after injection in all but one case, Chi-1. 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.

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 P₂, P₃, and P₄ (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, dog, and man — 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. Plasma clearance of pre-equilibrated Fe-transferrin has an average half-time of 96 minutes. 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 and 96% by the seventh hour in the dog — 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. Percent Pu per ml plasma was converted to % Pu in total blood volume by using the blood volume for the beagle. Long-term data were obtained from Table I in Stover et al. Data for the sheep were read from Figure 3 of McClellan et al.
Fig. 2. Disappearance of Pu from the blood of man, dog, and sheep. Dog data are from Stover et al., all dose levels combined; sheep data are from McClellan et al.
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/λ, 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 Λ, 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, 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. 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 and excreta 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 P₂ [PS₂ (normal) = 12.9 ± 3.6 hour, and PS₂ (impaired) = 19.1 ± 2.5 hour] were significantly different (P = 0.01). Component P₃ was slower in the persons with poor circulation, but the difference was not significant. No effect of circulatory impairment on component P₄ was detected, suggesting that this and later components are only minimally influenced by circulatory status. Intercepts PA₅, PA₇, and PA₉ 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 P₁) were probably also slowed by circulatory impairment.
Table III. Intercepts and half-times of unanalyzed semilogarithmic curves of Pu in human muscle, Pu(IV) citrate injected intravenously.

<table>
<thead>
<tr>
<th>Case</th>
<th>Day of last sample</th>
<th>PA&lt;sub&gt;1&lt;/sub&gt; (%)</th>
<th>PS&lt;sub&gt;1&lt;/sub&gt; (min)</th>
<th>PA&lt;sub&gt;2&lt;/sub&gt; (%)</th>
<th>PS&lt;sub&gt;2&lt;/sub&gt; (hr)</th>
<th>PA&lt;sub&gt;3&lt;/sub&gt; (%)</th>
<th>PS&lt;sub&gt;3&lt;/sub&gt; (days)</th>
<th>PA&lt;sub&gt;4&lt;/sub&gt; (%)</th>
<th>PS&lt;sub&gt;4&lt;/sub&gt; (days)</th>
<th>Circulation status&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP-1</td>
<td>10</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>53</td>
<td>18</td>
<td>30</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>55</td>
<td>16</td>
<td>26</td>
<td>1.6</td>
<td>5.6</td>
<td>7.4</td>
<td>Cardiac failure&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32</td>
<td>22.7</td>
<td>22</td>
<td>1.8</td>
<td>3.5</td>
<td>6.0</td>
<td>Edema&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>—</td>
<td>—</td>
<td>100</td>
<td>18.5</td>
<td>44</td>
<td>2.2</td>
<td>13.0</td>
<td>5.5</td>
<td>Hypertension&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>43</td>
<td>8.5</td>
<td>15</td>
<td>0.8</td>
<td>1.1</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>46</td>
<td>11.5</td>
<td>22</td>
<td>1.0</td>
<td>2.4</td>
<td>4.5</td>
<td>0.29</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37</td>
<td>20</td>
<td>24</td>
<td>2.0</td>
<td>3.6</td>
<td>6.0</td>
<td>0.48</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>45</td>
<td>14.5</td>
<td>22</td>
<td>1.7</td>
<td>4.3</td>
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<td>0.24</td>
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<td>9</td>
<td>36</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>51</td>
<td>12</td>
<td>16</td>
<td>2.6</td>
<td>6.9</td>
<td>6.6</td>
<td>0.58</td>
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<td>10</td>
<td>30</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60</td>
<td>18.5</td>
<td>33</td>
<td>2.3</td>
<td>4.8</td>
<td>6.8</td>
<td>0.49</td>
</tr>
<tr>
<td>12</td>
<td>46</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.64</td>
</tr>
</tbody>
</table>

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 |

<sup>a</sup> Status of circulation obtained from case histories.<sup>9</sup>
<sup>b</sup> Fitted to 100% at t = 0, and to 65% at t = 30 min.
<sup>c</sup> HP-2: "Essential hypertension with hypertensive cardiovascular disease and coronary insufficiency."
<sup>d</sup> HP-3: "Hepatitis with hypoproteinemia and dependent edema."
<sup>e</sup> HP-4: "Cushing's syndrome with hypertension, hypertensive heart disease."
<sup>f</sup> HP-5: "Rheumatic heart with mitral insufficiency and auricular fibrillation, hospitalized for cardiac decompensation."
<sup>g</sup> HP-10: "Acute congestive heart failure."
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. Additional excretion data for Chi-1, Chi-3, and Cal-1 through 155, 163, and 341 days, respectively, were available in the original references. 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. 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.
Table IV. Disappearance from circulating blood of intravenously injected Pu(IV) citrate. Parameters of equations 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.

<table>
<thead>
<tr>
<th>Species</th>
<th>Day of last sample</th>
<th>P_{α_{1}} (%)</th>
<th>P_{τ_{1}} (min.)</th>
<th>P_{α_{2}} (%)</th>
<th>P_{τ_{2}} (hr)</th>
<th>P_{α_{3}} (%)</th>
<th>P_{τ_{3}} (days)</th>
<th>P_{α_{4}} (%)</th>
<th>P_{τ_{4}} (days)</th>
<th>P_{α_{5}} (%)</th>
<th>P_{τ_{5}} (days)</th>
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<tr>
<td>Rat</td>
<td>8</td>
<td>60.3</td>
<td>58</td>
<td>37.3</td>
<td>8.2</td>
<td>0.8</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Dog^c</td>
<td>5</td>
<td>45</td>
<td>3-111</td>
<td>20.5</td>
<td>7.8</td>
<td>44</td>
<td>1.7</td>
<td></td>
<td></td>
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<td>14</td>
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<tr>
<td>Dog</td>
<td>3,000</td>
<td>44</td>
<td>11-48</td>
<td>19.5</td>
<td>7.3</td>
<td>30</td>
<td>1.0</td>
<td>2.1</td>
<td>5.0</td>
<td>0.081</td>
<td>220^a</td>
<td>28, 29</td>
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<td>10</td>
<td>68</td>
<td>24</td>
<td>25</td>
<td>2-5</td>
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<td>1.6</td>
<td>1.1</td>
<td>4.9</td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>Pig</td>
<td>475</td>
<td>52.4</td>
<td>20</td>
<td>27.1</td>
<td>7.3</td>
<td>17.2</td>
<td>1.2</td>
<td>3.3</td>
<td>5.0</td>
<td>0.44</td>
<td>230^a</td>
<td>40</td>
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<tr>
<td>Man^a</td>
<td>42</td>
<td>52.4</td>
<td>20</td>
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<td>17.2</td>
<td>1.2</td>
<td>3.3</td>
<td>5.0</td>
<td>0.44</td>
<td>230^a</td>
<td>40</td>
</tr>
</tbody>
</table>

^a P_{τ_i} (%) = \sum_{w=1}^{n} P_{α_w} \exp (-0.693t/P_{τ_w}).

^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_{α_{2}} = 0.045%, P_{τ_{2}} = 5500 days^a.

^e Average of two components: P_{α_{1}} = 0.41%, P_{τ_{1}} = 66 d; P_{α_{2}} = 0.33%, P_{τ_{2}} = 380 d.
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.\(^4\)

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.\(^5\)

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\(^5\) 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.\(^36\) 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
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 V) 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, UA1 and UA2, of the Pu urine curves of the presumably normal persons were almost twice as large as UA1 and UA2 determined for the anemic cases. UA3 of the normal group was substantially lower than UA3 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, UA1, of the Pu(VI)-injected cases was greater, and the half-time, US1, 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 that Pu(VI) protein binding is more stable than that of Pu(IV). The average intercepts and half-times of U3, U5, and U6 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.
Fig. 3. Daily urinary Pu excretion by several Pu-injected persons, dogs and miniature swine. Swine data are from Clarke et al.; dog data are from B. J. Stover and D. R. Atherton (original data) 0.1 μCi/kg groups 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 US1. 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 US3 and US5. Only Chi-3 and Cal-1, who were both injected with Pu(VI), provide any estimate of US1, 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, US3, 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 US5 in the Pu urine curve of the dog. US3 and US5 were not defined for HP-6 because collections were terminated too soon, but if US5 and US1 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 US5 should be greater than 1250 days.

Some long-term urine data from four occupationally exposed persons are shown in Figure 4: T.VBG, DLW, and WA4B, from whom urine specimens were obtained periodically for as long as 1698 days after termination of Pu exposure; and LASL-1 who was followed for 3500 days after cessation of his initial high level Pu exposure. 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 US5 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. These averages were not weighted for the number of analyses, and zero values were ignored.
Table V. Intercepts and half-times of unanalyzed human urine Pu curves.

<table>
<thead>
<tr>
<th>Case</th>
<th>Day of last sample</th>
<th>UA_1%/day</th>
<th>US_1 days</th>
<th>UA_2%/day</th>
<th>US_2 days</th>
<th>UA_3%/day</th>
<th>US_3 days</th>
<th>UA_4%/day</th>
<th>US_4 days</th>
<th>UA_5%/day</th>
<th>US_5 days</th>
<th>UA_6%/day</th>
<th>US_6 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pu (IV) citrate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>HP-2</td>
<td>34</td>
<td>0.58</td>
<td>1.9</td>
<td>0.105</td>
<td>8</td>
<td>0.0098</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HP-3</td>
<td>23 (1,610)*</td>
<td>0.76</td>
<td>1.1</td>
<td>0.270</td>
<td>2.8</td>
<td>0.0205</td>
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</tr>
<tr>
<td>HP-5a</td>
<td>22</td>
<td>0.40</td>
<td>1.1</td>
<td>0.050</td>
<td>9.3</td>
<td>0.0240</td>
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</tr>
<tr>
<td>HP-6a</td>
<td>22 (1,698)*</td>
<td>0.35</td>
<td>2.1</td>
<td>0.092</td>
<td>6.5</td>
<td>0.017b</td>
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<tr>
<td>HP-8</td>
<td>65</td>
<td>0.46</td>
<td>1.2</td>
<td>0.148</td>
<td>5.1</td>
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<tr>
<td>HP-10</td>
<td>30</td>
<td>0.55</td>
<td>1.9</td>
<td>0.162</td>
<td>5</td>
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</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.54*</td>
<td>1.65</td>
<td>0.138</td>
<td>6.1</td>
<td>0.0189</td>
<td></td>
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</tr>
<tr>
<td>±S.D.</td>
<td>0.12</td>
<td>0.44</td>
<td>0.05</td>
<td>2.3</td>
<td></td>
<td>0.006</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Anemic</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>HP-1</td>
<td>25</td>
<td>0.21</td>
<td>2.7</td>
<td>0.097</td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td>HP-7</td>
<td>37</td>
<td>0.28</td>
<td>2.6</td>
<td>0.044</td>
<td>9</td>
<td>0.0100*</td>
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<tr>
<td>HP-9</td>
<td>36</td>
<td>0.24</td>
<td>1.2</td>
<td>0.100</td>
<td>5.0</td>
<td>0.0400</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HP-12</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.24</td>
<td>2.1</td>
<td>0.088</td>
<td>7.6</td>
<td>0.0277</td>
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<td></td>
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<tr>
<td>±S.D.</td>
<td>0.03</td>
<td>0.58</td>
<td>0.03</td>
<td>1.6</td>
<td>0.005</td>
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### Abnormal kidney

<table>
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<tr>
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<th>HP-4</th>
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<tbody>
<tr>
<td></td>
<td>26</td>
<td>0.50</td>
<td>1.9</td>
<td>0.200</td>
<td>7.</td>
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### Pu (VI) citrate or PuO₂(NO₃)₉

**Anemic**

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<table>
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<tr>
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<tr>
<td>Cal-1</td>
<td>341</td>
<td>0.60</td>
<td>1.0</td>
<td>0.180</td>
<td>4.6</td>
<td>0.012</td>
<td>71</td>
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<tr>
<td>Chi-1</td>
<td>155</td>
<td>2.53</td>
<td>0.33</td>
<td>0.220</td>
<td>3.6</td>
<td>0.035</td>
<td>67</td>
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<tr>
<td>Chi-2</td>
<td>15</td>
<td>0.27</td>
<td>1.4</td>
<td>0.058</td>
<td>8.0</td>
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</table>

**Mean**

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<table>
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<tbody>
<tr>
<td>Mean</td>
<td>1.22</td>
<td>0.86</td>
<td>0.124</td>
<td>6.3</td>
<td>0.0223</td>
<td>60</td>
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**±S.D.**

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</thead>
<tbody>
<tr>
<td>±S.D.</td>
<td>1.01</td>
<td>0.45</td>
<td>0.089</td>
<td>2.6</td>
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**No information**

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<th>Chi-3</th>
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<tbody>
<tr>
<td>164</td>
<td>1.50</td>
<td>0.7</td>
<td>0.038</td>
<td>9.</td>
<td>0.020</td>
<td>42</td>
</tr>
</tbody>
</table>

* Renal function and erythropoiesis judged to be within normal limits.
* Estimated from constructed curves shown in Appendix 2abc. US, of HP-6 defined by two points at 525 and 1,610 days.**
* Single samples taken at these late post-injection intervals.*
* No published hematologic data, but presumed to be within normal limits.
* Underlined means were compared with the means immediately below by use of the t-test and "p" ≤ 0.05.*
* Kidneys abnormal.

* Both renal and hematopoietic function can be impaired in the advanced stages of Hodgkin's disease. (Included in Pu(VI) group mean.)
Table VI. Urinary and fecal excretion of Pu by adult man, young adult beagle, and adolescent miniature swine. Parameters of exponential excretory equations.a

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_1$</th>
<th>$\tau_1$</th>
<th>$\alpha_2$</th>
<th>$\tau_2$</th>
<th>$\alpha_3$</th>
<th>$\tau_3$</th>
<th>$\alpha_4$</th>
<th>$\tau_4$</th>
<th>$\alpha_5$</th>
<th>$\tau_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%/day</td>
<td>days</td>
<td>%/day</td>
<td>days</td>
<td>%/day</td>
<td>days</td>
<td>%/day</td>
<td>days</td>
<td>%/day</td>
<td>days</td>
</tr>
<tr>
<td>Normal Man</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine b</td>
<td>0.41</td>
<td>1.2</td>
<td>0.12</td>
<td>5.5</td>
<td>0.013</td>
<td>42</td>
<td>0.003</td>
<td>300</td>
<td>(0.0012)$^d$</td>
<td>(4,000)$^d$</td>
</tr>
<tr>
<td>Feces c</td>
<td>0.60</td>
<td>2.0</td>
<td>0.16</td>
<td>6.6</td>
<td>0.012</td>
<td>56</td>
<td>(0.002)$^d$</td>
<td>380</td>
<td>(0.0012)$^d$</td>
<td>(4,000)$^d$</td>
</tr>
<tr>
<td>Dog a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>4.6$^f$</td>
<td>0.48$^f$</td>
<td>0.15</td>
<td>3.3</td>
<td>0.008</td>
<td>450</td>
<td>0.004</td>
<td>3,850</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feces</td>
<td>3.0</td>
<td>2.3</td>
<td>0.31</td>
<td>4.6</td>
<td>0.08</td>
<td>14</td>
<td>0.007</td>
<td>350</td>
<td>0.0046</td>
<td>3,850</td>
</tr>
<tr>
<td>Swine a</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Urine</td>
<td>0.48</td>
<td>0.60</td>
<td>0.23</td>
<td>2.5</td>
<td>0.05</td>
<td>10</td>
<td>0.042</td>
<td>380</td>
<td></td>
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<tr>
<td>Feces</td>
<td>0.37</td>
<td>1.5</td>
<td>0.18</td>
<td>10</td>
<td>0.012</td>
<td>325</td>
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</tr>
</tbody>
</table>

a $U(t) \ (%/day)$ or $F(t) \ (%/day) = \sum_{n=1}^{n} a_n \exp(-0.693t/\tau_n)$.

b Kidney function and hematopoiesis presumed to be within normal limits.
c Liver and digestive tract function presumed to be within normal limits.
d Estimated.
e S. Stover et al.$^23$ and B. J. Stover and D. R. Atherton, original data: 0.1$\mu$Ci/kg and 0.5$\mu$Ci/kg groups only.
f Average of two components $U_n = 4.1%/day$, $U_m = 0.2$ day; $U_n = 1.9%/day$, $U_m = 0.8$ day.
g Data read from Figure 1 of Clarke et al.$^a$.
Fig. 4. Comparison of urinary excretion rates of four occupationally exposed persons and the rates predicted by the exponential Pu urine curve constructed in this paper (bold line) and the Langham equation (dashed line). Occupationally exposed persons: O — W.B.G., ⃞ — D.L.W., □ — W.A.B.; ● — LASL-1. Injected persons: ■ — HP-3 and ▲ — HP-6.
Lagerquist et al. reported an accident involving contamination of a Pu worker designated RF-2075 (S. E. Hammond, private communication). He inhaled some Pu, and his body surface was contaminated, but the bulk of his internal burden was apparently the result of Pu embedded in an injured hand. Twelve days after the accident 98% of the Pu in his hand was removed surgically, and he could be considered to have had a single acute exposure.

The urinary Pu excretion of RF-2075 is plotted in Figure 5 from data read off the published curves. This is a complicated case; the individual was treated almost continuously with DTPA, and three operations were performed to remove the Pu from his hand. Figure 5 shows, however, that the raw half-times of his Pu urine curve are very close to those obtained from the urine curves of the Pu-injected persons (see Table V). On the
other hand, the intercepts of the Pu urine curves of RF-2075 and the Pu-injected cases are quite different, reflecting the changes in Pu deposition pattern brought about by prolonged DTPA treatment.

The values selected for UA₁ and UA₂ in the human urinary curve were those determined for the Pu(IV)-injected persons with presumably normal kidneys and hematopoiesis. The intercepts of the curves obtained from the Pu(VI)-injected series were rejected throughout, because the four persons in that series met one or more of the criteria for altered urinary Pu excretion.

No Pu(IV)-injected individual provided urine data after 65 days post injection; however, a third component, U₃, emerged early enough in the curves of four cases to identify UA₃. The last few points on the curves of four additional cases suggested an inflection and permitted estimation of UA₃.

Only Cal-1 was followed long enough to identify the intercept, UA₄. Comparison of his daily urinary Pu, 0.0011 %/day between 300 and 350 days post injection, with the urinary Pu of HP-6, 0.002 %/day at 525 days and 0.0011 %/day at 1610 days post injection, suggests that the value of UA₄ obtained from Cal-1 is low by at least a factor of two. Consequently, the graphic construction method shown in Appendix 2 for HP-6 was used to estimate UA₄ and UA₅. Details of the construction are reported elsewhere.¹⁴

Gastrointestinal excretion of plutonium

The original Pu fecal excretion data for Chi-1 and HP-1 through HP-12 are given in Table 9 of Langham et al.¹⁹ Fecal Pu for Cal-1 was read from Figure 1 of Crowley et al.²⁵ Urine and feces were not separated for Chi-2, and fecal data were not reported for Chi-3.

As discussed in the preceding sections, Pu transport in blood and Pu filtration by the kidney are largely determined by Pu binding to transferrin. The small gastrointestinal elimination of Pu by larger animals can also be better understood in light of the stability of the complexes of Fe and Pu with transferrin and the high degree of conservation of iron. The human gastrointestinal tract normally excretes approximately 0.6 mg/day of iron.²⁶,²⁷,²⁸ Recent studies²⁹ indicate that secretion in bile accounts for 33% of fecal excretion, and loss of iron contained in the 50 to 80 g of intestinal epithelial cells that are desquamated daily accounts for another 13%. The remaining 40% of gastrointestinal iron excretion may
be associated with other digestive secretions (gastric, pancreatic, and intestinal juices).

Crosby suggests that the gastrointestinal tract is also an important site of transferrin catabolism.

It was suggested that early urinary Pu excretion was related in a roughly reciprocal way to the level of transferrin saturation. By the same line of reasoning, at least two of the proposed gastrointestinal excretory mechanisms — biliary and digestive-juice secretion — might also be expected to be influenced by the degree of digestive tract secretion. If dietary intake were low or consisted of soft, bland, nonstimulating foods, the volume of digestive secretions might be lower and fecal Pu consequently reduced.

During the first two weeks after injection some individuals consistently excreted more Pu in their feces than did others. In order to determine whether fecal Pu was related to medical status, fecal Pu was summed for each patient over the first and last 6-day intervals for which fecal collections were obtained from all the patients. Gastrointestinal tract and liver function and the amounts and varieties of foods eaten were judged to be within normal limits for six Pu(IV)-injected patients. Three patients were being treated for peptic ulcers and were probably taking small meals of soft bland foods to reduce gastrointestinal stimulation and secretion. After a total gastrectomy on the fourth day following his Pu injection, Cal-1 passed little fecal matter through day 17. Two patients were being treated for severe cardiac conditions, and it was considered likely that they too were taking in less than normal amounts of food and liquids. HP-3 was being treated for hepatitis, and the presence of pruritic dermatitis strongly suggests that she was also jaundiced and that her bile output was less than normal. Chi-1 was operated on twice (15 days before and 2 days after his Pu injection) to remove tumorous tissue from his buccal cavity. His output of fecal matter was normal shortly after injection, but as his condition deteriorated, the buccal lesion ulcerated to the bone, apparently making intake of ordinary foods difficult. After the hundredth day his fecal bulk was below the lower limit of normal.

If only the Pu(IV)-injected cases are considered, the average fecal Pu of those persons judged to have normal gastrointestinal function and normal dietary intakes was 1.32% ± 0.30, nearly twice that of the persons with gastrointestinal difficulties or restricted dietary intakes, 0.67% ± 0.14. The difference was significant (P<0.01) during the first 6 days after injection, but of only borderline significance between 19 and 24
days post injection; normal diet, 0.20% ± 0.08; restricted diet, 0.09% ± 0.04 (P=0.05). There were no discernible correlations between fecal Pu excretion and erythropoietic status.

The original fecal Pu data are plotted along with the urine curves in Appendix 2. Analysis of the early portions of most of these curves was not possible, because feces were sampled as 2- to 6-day pools. A cumulative fecal excretion curve was prepared for each case plotted as a linear function of time. Fecal lag — that is, gastrointestinal transit time — was estimated for each case by extrapolating the earliest defined portion of the cumulative curve to % dose/day = 0. The differentiated cumulative fecal Pu curves were replotted on a semilogarithmic scale (not shown), and the unanalyzed half-times, intercepts (at t = fecal lag), and fecal lag times for each case are collected in Table VII. The fecal Pu curves of the three persons who were followed for the longest time after injection, and the best curves that could be drawn for fecal excretion of Pu by the dog and the pig are shown in Figure 6.

The means ± standard deviation of the unanalyzed half-times and intercepts were calculated (see Table VII) for the six Pu(IV)-injected individuals that were presumed to have normally functioning gastrointestinal tracts and to be eating ordinary amounts of a mixed hospital diet and for the five Pu(IV)-injected persons judged to be taking in less than normal amounts of food or to be on soft diets (including HP-3, who was judged to have a lower-than-normal bile output). The half-times of the first two components of the normal Pu fecal curve are the averages of FS₁ and FS₂ determined for all the cases, because neither the medical status of the individuals nor the chemical form of Pu administered appeared to change the rates of the processes leading to these fecal-curve components.

FS₃ could be determined only for HP-7, Chi-1, and Cal-1. There was good agreement among the three and all were used to calculate an average FS₃. FS₄ observed only for Cal-1 emerged in his fecal curve only 100 days before collections were terminated, so it is uncertain. However, this portion of the Cal-1 fecal curve was almost parallel to the urine curve, US₄ = 475 days, which is encouraging. The value chosen for FS₅, 4000 days, was obtained by least-squares-fitting the fecal data of the 0.1 μCi/kg group of Utah dogs from 750 through 1750 days post injection.*

* Feces were collected periodically from some of the 0.1 μCi/kg dogs for as long as 2921 days. Data for individual dogs as well as the mean values of all survivors exhibited a rising trend after 1800 days.
Table VII. Half-times and intercepts of unanalyzed differentiated cumulative fecal Pu curves.

<table>
<thead>
<tr>
<th></th>
<th>Day of fecal lag&lt;sup&gt;b&lt;/sup&gt; (days)</th>
<th>FA&lt;sub&gt;1&lt;/sub&gt; (%/day)</th>
<th>FS&lt;sub&gt;1&lt;/sub&gt; (days)</th>
<th>FA&lt;sub&gt;2&lt;/sub&gt; (%/day)</th>
<th>FS&lt;sub&gt;2&lt;/sub&gt; (days)</th>
<th>FA&lt;sub&gt;3&lt;/sub&gt; (%/day)</th>
<th>FS&lt;sub&gt;3&lt;/sub&gt; (days)</th>
<th>FA&lt;sub&gt;4&lt;/sub&gt; (%/day)</th>
<th>FS&lt;sub&gt;4&lt;/sub&gt; (days)</th>
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<tbody>
<tr>
<td>Pu(IV) citrate</td>
<td>Normal diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HP-2</td>
<td>27</td>
<td>2</td>
<td>0.62</td>
<td>2.5</td>
<td>0.16</td>
<td>10.9</td>
<td>0.012</td>
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<tr>
<td>HP-4</td>
<td>82</td>
<td>1</td>
<td>0.75</td>
<td>3.1</td>
<td>0.35</td>
<td>6.0</td>
<td>6.7</td>
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<tr>
<td>HP-5</td>
<td>22</td>
<td>1.5</td>
<td>1.50</td>
<td>0.7</td>
<td>0.17</td>
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<td>HP-6</td>
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<td>1.5</td>
<td>0.60</td>
<td>1.2</td>
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<td>0.55</td>
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<td>HP-12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>46</td>
<td>1.5</td>
<td>0.60</td>
<td>2.0</td>
<td>0.072</td>
<td>16.0</td>
<td>0.020</td>
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</tr>
<tr>
<td>Mean</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>± S.D.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reduced liver function</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HP-3</td>
<td>23</td>
<td>2.0</td>
<td>0.24</td>
<td>2.7</td>
<td>0.082</td>
<td>7.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet Type</td>
<td>Cal-1(^a)</td>
<td>Cal-2(^a)</td>
<td>Cal-3(^a)</td>
<td>Cal-4(^a)</td>
<td>Mean(^d) ± S.D.</td>
<td></td>
<td></td>
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<tr>
<td>Restricted diet</td>
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<td>0.18</td>
<td>4.6</td>
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<td>650</td>
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<tr>
<td>Diet not known</td>
<td>138</td>
<td>1.0</td>
<td>1.00</td>
<td>1.3</td>
<td>0.18</td>
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<td></td>
<td>7.0</td>
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<td></td>
<td></td>
<td>85</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>0.0018</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

\(^a\) Intercept at \( t = \) fecal lag.

\(^b\) Fecal lag determined by extrapolation of cumulative fecal curve.

\(^c\) Anemic.

\(^d\) Includes HP-3.

\(Pu(VI)\) citrate or nitrate
Fig. 6. Daily fecal Pu excretion by Pu-injected persons, dogs, and miniature swine. Dog data are from B. J. Stover and D. R. Atherton (original data) 0.1 μCi/kg and 0.3 μCi/kg groups only; swine data are from Clarke et al.10
The intercepts of the first two components of the fecal Pu curves of the persons with normal digestive function were almost double those of FA₁ and FA₂ calculated for the persons having reduced gastrointestinal function, but the differences were not statistically significant. However, the intercepts of the first two components of the normal fecal Pu curve are the mean values of FA₁ and FA₂ determined for only those persons whose gastrointestinal tracts were judged to be normally stimulated and normally functional. FA₃ is the mean of the four Pu(IV)-injected cases for whom that parameter could be estimated.

Values for FA₄, the intercept of the longest observed component, were available from only two Pu(VI)-injected persons, neither of whom was considered to have a normally functioning gastrointestinal tract. The last 40 days of fecal collections from Chi-I were only one-half normal bulk and he was near death from metastases of his malignancy. FA₃ of his fecal curve was one-half that either observed or estimated for the less seriously ill Pu(IV)-injected persons. FA₃ from the fecal curve of Cal-I was even lower --- slightly more than 50% of FA₃ for Chi-I, and 20% of the average FA₃ of the Pu(IV) group. His stomach had been completely removed four days after the Pu injection. In the absence of a stomach, his daily food intake was probably low, and gastric juice --- which makes up a significant fraction of the total volume of digestive secretions --- was absent. Gastric acid is one of the normal stimulants of the secretion of bile, pancreatic and intestinal juices, and intestinal mucus. Iron absorption is reported to be reduced by as much as 50% after gastrectomy. Lack of gastric juice may have played an indirect as well as a direct role in reducing the quantity of gastrointestinal secretions and concomitantly the amount of Pu excreted in feces by Cal-I.

It was assumed that the relationships between the FA₄'s of Chi-I and Cal-I and the Pu(IV)-injected group, FA₁(Chi-I) = 0.5 FA₁(Pu(IV)) and FA₁(Cal-I) = 0.21 FA₁(Pu(IV)), could be used to estimate FA₄ for the Pu(IV)-injected group as follows:

$$FA₄ = [(0.0018/0.5) + (0.0056/0.21)] / 2 = 0.003 \% / \text{day}.$$  

An approximation of FA₅ was obtained by assuming that F₅ in the human curve and in the dog curve emerged at about the same time post injection. F₅ was extrapolated to that time (900 days), a line of 3850-day

* There is a possibility that systematic errors in collection and analysis also contributed to the low fecal Pu values of Cal-I.  

*0017283*
half-time was drawn through the 900-day point, and its intercept was determined to be 0.0012 %/day. The parameters of the five-component "normal" human fecal excretion curve appear in Table VI.

Urinary and Fecal Clearance of Plutonium

Having no fecal data beyond 138 days, Langham et al. were forced to use an estimate of the Pu U/F ratio to calculate long-term Pu excretion. However, both terms of the U/F ratio are subject to change, and clues to the nature of some changes — either in excretory efficiencies or in the chemical state of circulating Pu — can be obtained from plasma clearances. Accurate determination of urinary clearance requires simultaneous sampling of plasma and bladder urine. In the absence of precise measurements for man, Equations (4) and (5) were used to estimate excretory clearances from the data available for man, namely, intermittent plasma samples, 24-hour urine samples, and pooled fecal specimens.

\[
\text{Ex}_{\text{ur}} = \frac{t_2}{t_1} \text{Ex} \quad (4)
\]

\[
P(t) = \sum_{i=1}^{n} P_i = e^{-\lambda_i t}. \quad (5)
\]

Both urinary fecal clearances were calculated over 6-day intervals for as long as blood measurements were made, but only two intervals, at the beginning and the end of measurements, are shown.

Painter et al. measured urinary Pu clearances of dogs injected with acutely toxic doses of Pu(VI) citrate. Urinary clearance of Pu was very high 15 to 30 minutes post injection, but dropped rapidly to a minimum which persisted from 4 hours to the end of the first day. After the first day, urinary clearance rose slightly to a level that was sustained for the next 15 days.

The urinary Pu clearances calculated for man revealed a similar pattern. The very high initial clearance could not actually be demonstrated, because the earliest urine samples were pooled for the first 24 hours. However, the first 12 urine specimens passed by Chi-1 were analyzed separately, and 83% of the Pu excreted in the first 48 hours was passed in the first (0- to 6-hour) specimen. In the face of his rapidly declining blood level, this large urinary output would indicate a high initial Pu clearance.
In every case the average Pu clearances by the kidney and the gastrointestinal tract were lowest on the first day after injection (the minimum lasted through the third day for fecal clearance in some cases because of fecal lag). Clearance by either route rose to a temporary plateau of 5 to 15 days duration, and was followed by either another increase to a fairly stable plateau or a continued slow increase to the end of measurements between days 20 and 35. During the 2 weeks between the two sets of calculations both urinary and fecal clearances increased, so that by 19 to 24 days after injection, Pu excretion by either route was 3.7 times as efficient as it was during the first 6 days.

Renal Pu clearance in those persons judged to be anemic was less than one-half that in persons considered normal. Fecal clearance in those persons judged to have reduced digestive system function was less than one-half that of persons considered to have normally stimulated gastrointestinal tracts.

Urine to fecal ratios (U/F) were calculated for each case during the two intervals shown in Table VIII, using plasma clearances whenever possible. Of these 23 available U/F values, 13 were close to 1.0 (0.7 to 1.3); five were substantially less than 1.0 (0.3 to 0.6); and five were substantially more than 1.0 (1.4 to 2.2). The six U/F values obtained from the three persons judged to be most nearly normal with respect to both latent transferrin binding capacity and digestive system function were all less than 1.3. Of the five U/F values greater than 1.4, all were from persons with suppressed or impaired digestive system function. The long-term excretion data are only from Chi-1 and Cal-1, and their U/F results have been rejected for the same reason that their fecal excretion was considered low.

It appears that during the first 30 to 60 days after Pu injection the U/F ratio for those persons judged to be most nearly normal was about 1.0 and possibly as great as 1.3. The anemic cases with normal gastrointestinal function tended to have U/F values less than 1.0. Those persons with presumably normal plasma protein binding capacity but with reduced gastrointestinal function tended to have U/F values greater than 1.0. The anemic cases (in which protein binding capacity was presumed to be elevated and gastrointestinal secretion suppressed) exhibited reduced urinary and fecal clearances of Pu, and their U/F values were again close to 1.0.

Langham et al. used Pu U/F ratios varying from 1.8 at 138 days to 4.4 at 1750 days to estimate total long-term Pu excretion, but these
Table VIII. Renal and gastrointestinal clearance of circulating Pu. Clearances are expressed as fraction of circulating Pu.

<table>
<thead>
<tr>
<th>Renal Clearance</th>
<th>Fecal Clearance</th>
<th>(U/F)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groupb</td>
<td>1 to 6 days</td>
<td>19 to 24 days</td>
</tr>
<tr>
<td>HP-1 A</td>
<td>0.008</td>
<td>R</td>
</tr>
<tr>
<td>HP-2</td>
<td>0.017</td>
<td>0.031</td>
</tr>
<tr>
<td>HP-3</td>
<td>0.020</td>
<td>0.070</td>
</tr>
<tr>
<td>HP-4 Ab.K.</td>
<td>0.009</td>
<td>0.029</td>
</tr>
<tr>
<td>HP-5</td>
<td>0.021</td>
<td>0.098</td>
</tr>
<tr>
<td>HP-6</td>
<td>0.020</td>
<td>0.130</td>
</tr>
<tr>
<td>HP-7 A</td>
<td>0.011</td>
<td>0.025</td>
</tr>
<tr>
<td>HP-8</td>
<td>0.019</td>
<td>0.066</td>
</tr>
<tr>
<td>HP-9 A</td>
<td>0.007</td>
<td>0.034</td>
</tr>
<tr>
<td>HP-10</td>
<td>0.013</td>
<td>0.090</td>
</tr>
<tr>
<td>HP-12 A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kidney and erythropoiesis normal

<table>
<thead>
<tr>
<th>G.I. function normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>±S.D.</td>
</tr>
<tr>
<td>Anemia and/or abnormal kidneyb</td>
</tr>
<tr>
<td>Restricted diet and/or abnormal liver</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>±S.D.</td>
</tr>
<tr>
<td>&quot;P&quot;*</td>
</tr>
</tbody>
</table>

* U/F calculated from ratios of plasma clearance except for HP-12 and values obtained after 35 days for HP-8, which are ratios of summed excreta.
* Discussion of medical status groups in section on fecal excretion. R = restricted diet, Ab.L. = abnormal liver.
* T-test of Fisher."
U/F estimates were based entirely on data from Chi-1 and Cal-1, both of whom have been considered in this reanalysis to have subnormally stimulated or subnormally functioning gastrointestinal tracts. The analysis presented here suggests that immediately after injection in man, Pu excretion in feces slightly exceeded Pu excretion in urine, and that by the end of the second week excretion by the two routes was nearly equal, provided that residual transferrin binding, kidney function, liver function, and gastrointestinal secretion remained within normal limits. Comparison of the coefficients of the long-term components of the exponential urinary and fecal Pu-excretion equations (see Table VI) suggests that at times after Pu injection longer than 100 days, U/F for Pu in man probably lies between 1.0 and 1.5.

**Human plutonium excretion — comparison with previous analyses**

When excretion rates are expressed as sums of exponentials, urinary excretion at time t after injection is

\[ U_t \text{ (%/day)} = \sum_{n=1}^{n} U_{\alpha_n} e^{-0.693t/U_{\tau_n}}, \]  

and similarly, fecal excretion rate at time t is

\[ F_t \text{ (%/day)} = \sum_{n=1}^{n} F_{\alpha_n} e^{-0.693t/F_{\tau_n}}. \]

The total amount of Pu excreted in urine or feces at time t is obtained by integration of Equations (6) and (7).

\[ \Sigma U_t(\%) = \int_0^t U_t \, dt, \]  

\[ \Sigma F_t(\%) = \int_0^t F_t \, dt. \]

Total excretion at time t is the sum of Equations (8) and (9).

\[ \Sigma E_t \text{ (%)} = \Sigma U_t \text{ } + \Sigma F_t \]

and whole-body retention at time t is

\[ R_t \text{ (%)} = 100\% - \Sigma E_t. \]

The fraction of the remaining body burden excreted daily in urine at time t is

\[ U_b \text{ (%/day)} = (U_t \times 100)/R_t. \]

Urinary and fecal excretion rates (Figures 7 and 8), the total amount of Pu excreted in urine and feces (Table IX), whole body retention and
the fraction of the body burden excreted in a 1-day urine sample (Figure 9) were calculated for times after injection from 1 to 14,600 days (about 40 years), using Equations (6) through (12) and the parameters of the "normal" Pu urinary and fecal excretion equations given in Table VI. It was assumed for these calculations that a sixth component with a half-time of 13,400 days (see the discussion of case LASL-1 in the section on urinary excretion) emerged in both excretion curves about 4000 days after injection. Total Pu excretion after a single intravenous injection predicted by the sums of exponentials derived in this paper is compared in Table IX with that predicted by the power functions derived by Langham et al.19 Sums of exponentials predicted greater Pu elimination at all post-injection times for at least three reasons: (a) Exponentials fitted the first 10 days' data better than the power functions. (b) Only the individual urine-curve and fecal-curve coefficients from cases judged to be normal with respect to the particular excretory function were used to calculate the mean coefficients of the exponential equations, and they tended to be higher than the averages of all cases. (c) The coefficients of the exponential equa-

Fig. 7. Comparison of human urinary Pu excretion (from 1 day to 40 years) predicted by the normal Pu urine curve with the Langham equation.19 Points shown were calculated from the parameters in Table VI.
Fig. 8. Comparison of human fecal Pu excretion (from 1 day to 40 years) predicted by the normal Pu fecal curve and the equation given by Langham et al. Points shown were calculated from the parameters in Table VI.

Fig. 9. Comparison of the percent of the Pu body content excreted daily in the urine from 1 day to 40 years predicted by the normal Pu urine and fecal curves in this paper and the equations of Langham et al. Points shown were calculated from the parameters given in Table VI.
tion of human fecal excretion were adjusted upward to correct for what was considered to be unusually low long-term fecal elimination by Chi-1 and Cal-1.

Table IX. Comparison of long-term Pu excretion predicted from power functions or sums of exponentials.*

<table>
<thead>
<tr>
<th>Time after injection (days)</th>
<th>Power functions, Langham et al.</th>
<th>Sums of exponentials, this paper</th>
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</thead>
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<tr>
<td></td>
<td>(years)</td>
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</tr>
<tr>
<td>10</td>
<td>2.56</td>
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<td>20</td>
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<td>720</td>
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<td>12.17</td>
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<tr>
<td>14,600</td>
<td>40</td>
<td>22.49</td>
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* See Tables X and XIV for excretion equation parameters.

For comparison with earlier analyses, the urinary and fecal excretion rate equations are replotted logarithmically in Figures 7 and 8. At least three power functions were needed to describe these equations. The power function fitted to the calculated urinary excretion in the time period from 30 to 360 days was almost the same as that originally derived by Langham et al. from the raw averages of the data from the Pu-injected cases and some accidentally exposed persons and more recently reevaluated by machine curve fitting by Robertson and Cohn.

This paper,

\[ U_t (\%/\text{day}) = 0.17T^{-0.725} \quad (30 \leq T \leq 360 \text{ days}) \]

Langham et al.,

\[ Y_{ut}(\%/\text{day}) = 0.2X^{-0.74} \quad (10 \leq X \leq 1750 \text{ days}) \]

Robertson and Cohn,

\[ Y_u(\%/\text{day}) = 0.193t^{-0.721} \quad (1 \leq t \leq 1750 \text{ days}) \]
Figure 9 is the log-log plot of the fraction of the remaining Pu burden excreted daily in urine. The power function fitted to the time period $40 \leq T < 360$ days is nearly the same as that derived by Langham et al.\textsuperscript{19} using a different analytical method.

None of the power functions needed to fit the values of human Pu fecal excretion calculated from the exponential equation in Table VI agreed with the expression derived by Langham et al.\textsuperscript{19} Most of the difference between the two methods arises from the ways fecal data were handled and the assumptions about the long-term trend of fecal Pu output.

**Prediction of long-term whole-body plutonium retention**

The currently accepted maximum permissible $^{239}$Pu contents of the body of occupational workers, based on skeleton and liver, are 0.04 and 0.4 $\mu$Ci, respectively.\textsuperscript{39} For purposes of dose calculations biological half-lives are also given; $6.5 \times 10^4$ days (178 years) for whole body, $7.3 \times 10^4$ days (300 years) for skeleton, and $3 \times 10^4$ days (82 years) for liver.

The term “retention” is potentially misleading, because it suggests a static condition. Once deposited in a tissue, Pu would be understood to remain fixed until eliminated from the body altogether. Studies of pigs and dogs demonstrate the dynamic behavior of Pu. In the course of 600 days of growth remodeling, the skeletons of adolescent miniature swine\textsuperscript{41} released about 38\% of the injected Pu(IV) citrate dose (53\% of the 30-day bone deposit). Plasma Pu level and urinary excretion of Pu remained high. At 600 days the liver contained three times as much Pu (35\% of the dose) as it contained 30 days after injection (13\% of the dose).

At this writing there have been enough deaths of Utah dogs given 0.3 $\mu$Ci/kg or less to establish a long-term half-time for Pu in the beagle skeleton of more than 1500 days\textsuperscript{53} (perhaps as long as 5000 days). Bone remodeling in these 14- to 18-month-old dogs proceeded rapidly during the first two years but slowed thereafter. By 3 months post injection nearly one-half of the trabecular surfaces that had initially been labeled with Pu had disappeared. The remaining one-half had been buried by apposition of new bone, and were presumably less accessible for remodeling.\textsuperscript{94} At these same low dose levels, the half-time of Pu in the dog liver was about 3800 days.\textsuperscript{95} The prolonged residence in liver is the end result of a chain of events that carries Pu from plasma to Pu-ferritin in hepatic cells, and eventually to long-lived deposits of Pu-hemosiderin in reticuloendothelial cells.\textsuperscript{96-98}
Pu dynamics can be summarized as follows: Pu initially present in soft tissues other than liver is cleared rapidly; the major fraction is redistributed to bone and liver, and a small fraction is excreted. Pu deposited in the skeleton is mobilized in the normal course of bone remodeling; some is redeposited in bone, some is deposited in liver, and a small fraction is excreted. Pu deposited in liver is eventually transformed from relatively soluble forms in hepatic cells into insoluble hemosiderin deposits and sequestered in reticuloendothelial cells. Therefore, liver Pu is likely to be lost as slowly as, or more slowly than, bone Pu, but at perhaps the same rate as deposits of phagocytized Pu-hemosiderin in other tissues. The loss rate from the liver may eventually become the rate-limiting process for Pu disappearance from the whole body.

The best estimates of the early distribution of Pu in four major compartments—skeleton, liver, residual soft tissues, and excreta—are shown in Table X for man, dog, and pig. The original analysis of the tissue distribution data is included for comparison. The pigs were not fully grown and the dogs were in the prime of young adulthood, in contrast to the Pu-injected human beings who were all unwell and, except for HP-4, middle-aged or older. In the dog and pig only a small fraction of the Pu dose was in soft tissues other than liver (3% to 8%) 22 to 30 days after injection.

Table X. Early distribution of Pu in man, dog, and pig.

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Injected Pu (%)</th>
<th>Soft tissue remainder</th>
<th>Excreted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Man</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This paper</td>
<td>5 to 17 days</td>
<td>47.5</td>
<td>26.8</td>
</tr>
<tr>
<td></td>
<td>5 to 15 months</td>
<td>47.5</td>
<td>31.2</td>
</tr>
<tr>
<td>Langham et al</td>
<td>4 to 457 days</td>
<td>65.7</td>
<td>22.5</td>
</tr>
<tr>
<td><strong>Dog</strong></td>
<td>22 days</td>
<td>51.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Pig</td>
<td>30 days</td>
<td>72.0</td>
<td>14.0</td>
</tr>
</tbody>
</table>

* Average of Cal-1, Chi-2, HP-11. Cal-3. Livers and skeletons of Chi-2 and HP-11 not included. See Tables I and II.
  
* Averages of HP-5, HP-9, and Chi-1. See Tables I and II.
  
* Average of all tissues from all cases in Langham et al. Excretion estimated from power functions. Soft tissues calculated by difference.
  
* Stover et al.
  
* Skeleton from Clarke et al. Liver from Smith et al. Excreta calculated from exponential equations in Table VI. Soft tissue calculated by difference.
An average of 11.2% of the Pu dose was calculated to be in the soft tissues of the Pu-injected people who came to autopsy 5 to 15 months post injection. The large soft-tissue compartment in these middle-aged people compared with the smaller soft tissue compartment in the young vigorous animals may be a species difference, or it may be a real effect of age stemming from poorer circulation, more fibrous (less cellular) connective tissue, the presence of ectopic calcifications and fatty plaques, and reduced cell turnover that accompany advancing age.

Frost\textsuperscript{99} used a tetracycline labeling method and estimated the rate of bone replacement in rib and clavicle cortex of persons 35 to 70 years of age to be between 2.5%/year and 6%/year. Kulp et al.\textsuperscript{100} used fallout \textsuperscript{90}Sr analyses of individual bones and whole skeletons to obtain specific activity ratios (\textsuperscript{90}Sr in bone/\textsuperscript{90}Sr in skeleton) in adult human long-bone cortex, whole rib, and vertebrae. Bryant and Loutit\textsuperscript{101} calculated the annual rate of bone turnover required to produce those observed specific activities — 1.1%/year to 2.6%/year in whole femur, 2.1%/year to 6.2%/year in whole rib, and 5%/year to 10.4%/year in vertebrae. Rowland\textsuperscript{102} using an autoradiographic technique and bone from persons with long-standing burdens of \textsuperscript{226}Ra, calculated a turnover rate of 1.1%/year for long-bone cortex. All the above calculated turnover rates are in good agreement with each other.

The best estimates of the annual mass replacement rates of certain human bones are probably the mid-points of the ranges cited above — 1.85%/year for whole long bone, 4.2%/year for whole rib, and 7.7%/year for vertebrae. Pu is deposited on bone surfaces, and May\textsuperscript{103} has suggested that the surface of a mass of trabecular bone is four times the surface of an equal mass of cortical bone. Using a ratio of 4:1, for trabecular to cortical bone surface, estimating trabecular bone mass to be 23% of the total (ashed or dried) skeleton, and using the above estimates of bone turnover, one calculates the average turnover rate of the bone surface of the entire human skeleton to be 5%/year.

\[
\frac{(0.23 \times 4 \times 7.7\% / \text{year}) + (0.77 \times 1.85\% / \text{year})}{2} = 5\% / \text{year}.
\]

The associated half-time of the bone surfaces is 13.9 years, slightly less than the 15-year half-time observed in long-term \textsuperscript{226}Ra retention in man.\textsuperscript{104} Assuming that 50% of circulating Pu is redeposited in human bone,\textsuperscript{105} the observed half-time of Pu in the skeleton would be 88 years.\textsuperscript{*}

\* Since this paper was written, Nenot et al.\textsuperscript{106} have reported that Pu was deposited almost exclusively in the bone of rats injected intravenously with Pu(IV)-transferrin, and Durbin et al.\textsuperscript{107} concluded from a kinetic analysis of Pu(IV) citrate
(10,220 days), reasonably close to the 13,400-day half-time that could be fitted to the long-term urine data of case LASL-1.

The half-time of Pu in the human body was estimated in this analysis to be 204 years in substantial agreement with the upper limit calculated by Langham et al.\textsuperscript{15} The important consequence of Pu loss from bone faster than from the whole body is an increase in liver Pu with time.

Mays et al.\textsuperscript{16} have calculated that if the body Pu content were partitioned 50% in liver and 50% in bone, the annual risk of developing a liver tumor would be twice that of developing a bone tumor. The analysis in this paper suggests that over a 50-year working lifetime the liver's share of the body Pu content grows progressively larger, eventually approaching 50%. The consequences of this model and the calculations of Mays et al.\textsuperscript{16} are that liver is as critical an organ for Pu as is the skeleton.

DEDICATION

This chapter is dedicated to the memory of Dr. Burris B. Cunningham, Professor of Chemistry, University of California at Berkeley, and Senior Staff Scientist of the Department of Chemistry, University of California, Lawrence Radiation Laboratory, who with L. B. Werner first prepared plutonium in pure form and who developed on a micro-chemical scale the chemical techniques that were later used in the purification of large quantities of plutonium. I remember with pleasure and appreciation many conversations with Dr. Cunningham on matters of plutonium and actinide chemistry.

APPENDIX 1

Summary of Plutonium Cases

\textbf{HP-I}: White male, 67 yr, 70.3 kg, injected 10/16/45, 0.004 \(\mu\)Ci/kg \(^{239}\text{Pu}(IV)\) citrate. Nine year history of peptic ulcer, acute hemorrhage, Hb = 13.7, RBC = 4.5. Lost to follow-up.

\textsuperscript{16} The deposition in the rat that the rat skeleton accumulated both free and protein-bound Pu but that the rat liver did not take up significant amounts of protein-bound Pu. Inasmuch as at times greater than a few hours after injection more than 90\% of circulating Pu is protein bound,\textsuperscript{16} the deposition pattern of recirculated Pu is more likely to resemble that of Pu-transferrin than that of the Pu(IV) citrate originally injected. Thus, Pu redeposition in bone may be great as 80\% to 90\% leading to a longer calculated halftime of Pu in the human skeleton,\textsuperscript{16} about 70 years, and to a slower rate of Pu accumulation in the liver.
HP-2: White male, 49 yr, 69 kg, injected 10/23/43, 0.0045 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. Hemophilia, hypertension, cardiovascular disease. Hb = 14.5, RBC = 4.1. Lost to follow up.

HP-3: White female, 49 yr, 69.9 kg, injected 11/27/45, 0.0043 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. Hepatitis, pruritic dermatitis with edema, hypoproteinemia. Hb = 14.5, RBC = 4.3. Follow-up 1645 days post injection, lost thereafter.

HP-4: White female, 18 yr, 55.5 kg, injected 11/27/45, 0.0054 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. Cushing’s syndrome, hypertension, nephropathy with uremia, osteoporosis. Hb = 15.0, RBC = 5.3. Died 18 months post injection, autopsy withheld.

HP-5: White male, 56 yr, injected 11/30/45, \(~\) 0.0044 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. Amyotrophic lateral sclerosis, pneumonia, renal cysts and adenoma. Died 151 days post injection, autopsied.

HP-6: White male, 45 yr, injected 2/1/46, \(~\) 0.0044 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. One-year Addison’s disease, infected skin lesions. Follow-up 523 and 1610 days post injection, lost thereafter.

HP-7: White female, 59 yr, 68 kg, injected 2/8/46, 0.0057 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. Rheumatic heart disease, cardiac decompensation, toxic goiter. Hb = 12.6, RBC = 3.26. Died 9 months post injection, autopsy withheld.

HP-8: White female, 41 yr, 54.4 kg, injected 3/9/46, 0.0073 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. Two year history of duodenal ulcers and scleroderma. Hb = 13.9, RBC = 4.7. Lost to follow-up.

HP-9: White male, 66 yr, 63 kg, injected 4/3/46, 0.0061 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. 18-month history of muscular atrophy and dermatitis (dermatomyositis). Hb = 12.3, RBC = 3.9. Died 456 days post injection, of bronchopneumonia, autopsied.

HP-10: Negro male, 52 yr, 71 kg, injected 7/16/46, 0.0053 μCi/kg \(^{239}\text{Pu}\) (IV) citrate. Congestive heart failure. Hb = 13.3, RBC = 5.5. Lost to follow up.
HP-11: White male, 68 yr, injected 2/20/46, \( \sim 0.0056 \, \mu \text{Ci/kg} \) \(^{239}\text{Pu(IV)}\) citrate. History of chronic malnutrition and alcoholism. Died 5 days post injection, cirrhosis of liver, edema, ascites, autopsied.

HP-12: Negro male, 53 yr, injected 4/10/45, \( \sim 0.0044 \, \mu \text{Ci/kg} \) \(^{239}\text{Pu(IV)}\) citrate. Multiple comminuted fractures. Hb = 8.9, RBC = 2.85. Biopsy 4 days post injection, lost to follow-up. (Also designated E. C. in Ref. 18).

Chi-1: White male, 68 yr, 76.4 kg, injected 4/26/45, 0.0052 \( \mu \text{Ci/kg} \) \(^{239}\text{Pu(VI)}\) citrate. Metastasizing buccal epithelioma, mild pyelonephritis. Hb = 10.9, RBC = 3.56. Mouth surgery 2 days post injection. Died 160 days post injection, autopsied. (Also designated MX-100 in Ref. 48a).

Chi-2: White female, 55 yr, 38.6 kg, injected 12/27/45, 0.15 \( \mu \text{Ci/kg} \) \(^{239}\text{Pu(VI)}\) citrate. Metastasizing breast carcinoma and lymphoblastoma, both tumors invading liver, kidneys, and bone marrow, healing pathological rib fractures, Hb = 12, RBC = 3.5. Died 17 days post injection, autopsied. (Also designated WX-300 in Ref. 48b).

Chi-3: White male, young adult, injected 12/27/45, \( \sim 0.085 \, \mu \text{Ci/kg} \) \(^{239}\text{Pu(VI)}\) citrate. Hodgkin's disease, no other information. Died \( \sim 170 \) days post injection, autopsy withheld. (Also designated as MX-200 in Ref. 48).

Cal-1: White male, 58 yr, 58 kg, injected 5/14/45, 0.0896 \( \mu \text{Ci/kg} \) \(^{239}\text{Pu}, \) and 0.002 \( \mu \text{Ci/kg} \) \(^{238}\text{Pu as PuO}_2(\text{NO}_3)_2\). Diagnosed as gastric carcinoma, gastrointestinal hemorrhage. Hb = 12, RBC = 4.1. Biopsy 4 days p.i. revealed huge gastric ulcer and adhesions. Total gastrectomy and splenectomy. Followed for 340 days, died 1/9/66 (21 yr. post injection) of cardiovascular disease.

Case Cal-2a

This case, a 4-yr-10-month-old white male of slight build, was suffering from osteogenic sarcoma with pathologic fractures. He was injected 4/26/46 i.v. with 0.169 \( \mu \text{Ci} \) of \(^{239}\text{Pu(VI)}\) citrate, and tissue samples were obtained 7 days post injection during a biopsy. Body weight was estimated to be 15.5 kg from Mühlmann's tables \(^{107}\) and Bayer and Bayley's curve \(^{108}\) of retarded growth. Blood volume was estimated to be
7.5% of the body weight with a pcv = 0.4. Skeletal weight was estimated to be 2300 g, and the weight of the femora to be 0.125 of the skeletal weight from Theile's measurements of children's bones. Died, 1/6/47, no autopsy.

<table>
<thead>
<tr>
<th>Samples</th>
<th>Wet weight</th>
<th>% Dose</th>
<th>%/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>4.05</td>
<td>0.237</td>
<td>0.0585</td>
</tr>
<tr>
<td>Tumor and adjacent trabecular bone</td>
<td>3.7</td>
<td>0.129</td>
<td>0.0349</td>
</tr>
<tr>
<td>Tumor adjacent to cortex</td>
<td>3.7</td>
<td>0.59</td>
<td>0.159</td>
</tr>
<tr>
<td>Calcified tumor and muscle</td>
<td>0.61</td>
<td>0.0285</td>
<td>0.047</td>
</tr>
<tr>
<td>Soft tumor and muscle</td>
<td>0.92</td>
<td>0.00085</td>
<td>0.00092</td>
</tr>
<tr>
<td>Periosteum</td>
<td>0.65</td>
<td>0.00056</td>
<td>0.00086</td>
</tr>
<tr>
<td>Plasma - 1 hr</td>
<td>5.78</td>
<td>0.0043</td>
<td></td>
</tr>
<tr>
<td>Plasma - 4 days</td>
<td>.077</td>
<td></td>
<td>0.00063</td>
</tr>
</tbody>
</table>

Reconstruction of whole bone (femur)

\[
\frac{(0.237 + 0.00056 + 0.129)}{4.05 + 0.65 + 3.7} \times 100 = \frac{0.372}{8.4} = 0.0436\%/g
\]


Case Cal-3*

This case, a 73.3 kg, 36-yr old Negro male, was diagnosed from biopsy as having an osteo-fibro myxochondrosarcoma involving the distal femur, patella and proximal tibia. He was injected 7/18/47 with 0.095 \(\mu\)Ci \(^{239}\)Pu(VI) nitrate intramuscularly at an ink-marked location on the gastrocnemius muscle. A mid-thigh amputation was performed four days p.i. Alive and well 7/17/68, 21 yr. post injection.
<table>
<thead>
<tr>
<th>Samples</th>
<th>Wet wt. (g)</th>
<th>Ash wt. (g)</th>
<th>Percent of absorbed dose</th>
<th>Percent of absorbed dose/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>29.5</td>
<td>0.37</td>
<td>0.60</td>
<td>0.0203</td>
</tr>
<tr>
<td>Bone and tumor(^b)</td>
<td>31.5</td>
<td>12.6</td>
<td>0.144</td>
<td>0.0046</td>
</tr>
<tr>
<td>Marrow</td>
<td>4.0</td>
<td>0.05</td>
<td>0.063</td>
<td>0.0158</td>
</tr>
<tr>
<td>Normal cortex</td>
<td>50.5</td>
<td>20.0</td>
<td>0.063</td>
<td>0.00124</td>
</tr>
<tr>
<td>Muscle from normal bone</td>
<td>27.5</td>
<td>0.345</td>
<td>0.025</td>
<td>0.0009</td>
</tr>
<tr>
<td>Injection site</td>
<td>69.5</td>
<td>0.87</td>
<td>46.6(^a)</td>
<td></td>
</tr>
</tbody>
</table>

Whole femur reconstruction:

\[
\frac{(\text{Bone} + \text{tumor}) + (\text{marrow}) + (\text{normal cortex})}{(\text{Bone} + \text{tumor}) + (\text{marrow}) + (\text{normal cortex})} \times \text{g} = 0.00313\% \text{/g}
\]

\(^a\) Data of J. G. Hamilton and J. C. Cowley, unpublished.

\(^b\) Part of distal femur, patella, and proximal tibia.

\(^c\) \% of administered dose.
Appendix Fig. 2a. Original urine and fecal data of Pu(IV)-injected individuals HP-1, HP-2, HP-3, HP-4, HP-5, and HP-6.
Appendix Fig. 2b. Original urine and fecal data of Pu(IV)-injected individuals HP-7, HP-8, HP-9, HP-10, and Pu(VI)-citrate injected Chi-2.
Appendix Fig. 2c. Original urine and fecal data of Pu(VI) injected individuals Chi-1, Chi-3, and Cal-1.
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