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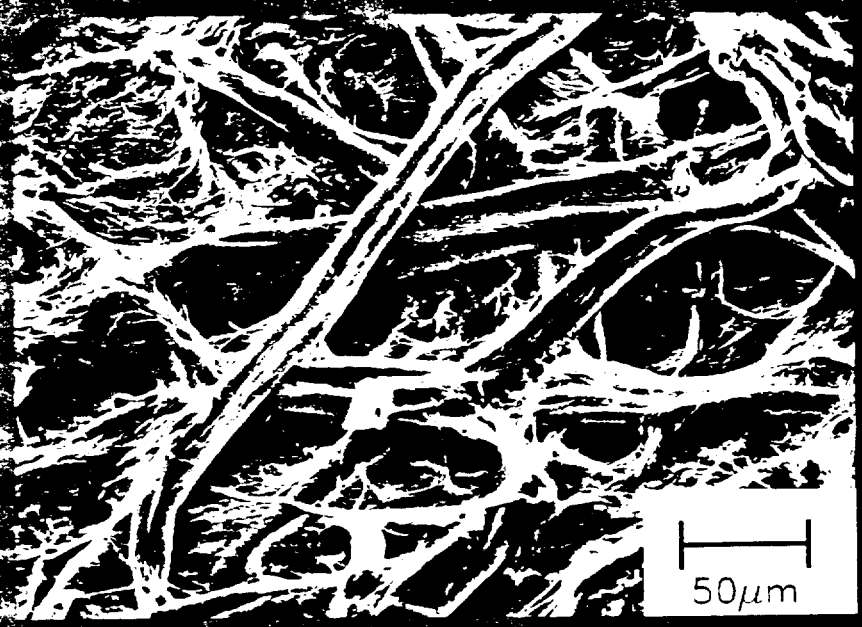
VOL. 65, NO. 1, JULY 1993

HEALTH PHYSICS

THE RADIATION PROTECTION JOURNAL

The Official Journal of
the Health Physics Society



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Paper

METABOLISM OF INJECTED PLUTONIUM IN TWO HEALTHY MEN

R. J. Talbot, D. Newton, and A. J. Warner*

***Abstract*—The metabolism of plutonium has been studied following intravenous injection of ^{237}Pu as Pu (IV) citrate into two healthy male volunteers. Measurements of the tracer in samples of blood and excreta were made by gamma-ray spectrometry, and patterns of organ uptake were investigated through serial measurements with a scintillation counter viewing the liver and selected skeletal sites. Excretion in urine and feces measured during the first 3 wk accorded closely with the patterns deduced by Durbin from the report of Langham et al. on patients injected with ^{239}Pu. However, concentrations in blood were roughly twice those suggested by Durbin during most of the 14 d covered by our measurements. In one subject, the liver deposit increased to a plateau after about 21 d, at roughly 55% of the injection; in the other, the increase was prolonged, reaching about 70% after several months.**
Health Phys. 65(1):41–46; 1993

Key words: metabolism; ^{239}Pu; ^{237}Pu; dosimetry, internal

INTRODUCTION

ROUTINE monitoring for internal contamination with plutonium is generally based on analysis of excreta, most commonly urine. Metabolic models are employed in translating observed excretion rates into estimates of initial or residual deposits. Models are also involved in setting the limits of intake for plutonium adopted by the International Commission on Radiological Protection (ICRP 1979) to control internal exposure. Current models (ICRP 1986, 1988) depend heavily on the reported behavior of ^{239}Pu injected into subjects with terminal prognoses (Langham et al. 1980) whose metabolism may have been affected by their medical condition (Durbin 1972).

It is obviously important to secure metabolic data appropriate to a healthy work force, but ^{239}Pu would deliver a prohibitive radiation dose if injected into volunteers in the quantities required for such a study. An alternative is to use ^{237}Pu (half-life 45.3 d), which can be produced by the reaction ^{235}U (^{4}He, 2n). Studies in rats have shown ^{237}Pu to be a valid metabolic tracer for the long-lived, alpha-emitting isotopes when injected as the citrate (Talbot et al. 1990). Essentially the same conclusions were reached by Lloyd et al. (1976) following injection into beagles: such differences as were noted were regarded by those authors as of marginal significance. The decay of ^{237}Pu is mainly (>99.99%) by electron capture and, in principle, as much as 100 kBq could be administered to volunteers, delivering a committed effective dose (CED) of only 100 μSv; moreover, the K x rays emitted during this decay would allow patterns of organ uptake to be studied with suitably located detectors. Previously, ^{237}Pu has not been used in this way because of difficulties in producing it sufficiently free of other isotopes of plutonium potentially delivering a much larger CED. However, careful selection of the conditions of irradiation has led to purer material (Talbot et al. 1990), allowing us to undertake a metabolic study following injection of ^{237}Pu into two healthy male subjects. In this account, we report the observed patterns of excretion, clearance from blood and major systemic uptake. Assessments of gonadal uptake by one of these subjects have already been reported (Newton et al. 1990).

MATERIALS AND METHODS

Harwell's variable-energy cyclotron was used to make ^{237}Pu by helium-ion irradiation of uranium highly enriched in ^{235}U, as described previously (Talbot et al. 1990). The ^{237}Pu separated from the target was dried and redissolved in 5 mL of 0.01-M nitric acid. An equal volume of 2% (w/v) trisodium citrate was added, and the resulting solution was passed through a membrane filter (pore size 0.025 μm) to remove any polymeric material. Before injection, the solution was diluted to approximately 300 Bq mL^{-1}, sterilized by ultrafiltration, and tested for pyrogenicity.

The subjects (Table 1) were healthy, hematologically normal males. Each received an injection of 1.4 kBq into an antecubital vein. The CED, based on the metabolic model adopted in ICRP Publication 30 (1979) but with the revised tissue-weighting factors recommended in Publication 60 (ICRP 1991), was 0.2 mSv; of this, >99% arose from 0.18 Bq ^{236}Pu and 0.30 Bq ^{238}Pu present as impurities.

Samples of venous blood (20 mL) were taken at intervals during the first 21 d for measurement of their ^{237}Pu content through its emitted K_α x rays (energies

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(*Manuscript received* 15 *July* 1992; *revised manuscript received* 2 *December* 1992, *accepted* 11 *January* 1993)
0017-9078/93/$3.00/0
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Table 1. Details of volunteers.

Subject	Weight (kg)	Height (m)	Age (y)	Hemoglobin (g dL^{-1})	PCV[a] (%)
A	88	1.88	62	14.2	42
B	58	1.52	70	13.7	42

[a] Packed cell volume.

98–101 keV) recorded using a shielded well-geometry semiconductor detector. There were also complete daily collections of excreta during this period, with more frequent sampling of urine during the first day. Individual fecal samples were dried and ashed. Plutonium was coprecipitated from each 24-h urine collection with $CaMg(PO_4)_2$; the precipitate was collected by filtration, dried, and ashed. The ^{237}Pu in ash from both urine and feces was estimated from spectra recorded with the well counter. Corrections for losses in processing the samples were assessed from determinations by alpha spectrometry of ^{242}Pu initially added as a yield tracer; these losses averaged 6% (urine) and 5% (feces).

The patterns of hepatic and skeletal uptake were monitored up to 153 d (maximum) after injection, with a 200-mm-diameter NaI(Tl)/CsI(Tl) scintillation counter (or "phoswich") reproducibly located close to the liver, sacrum, knees, and skull. The background response was minimized by housing the subject and detector inside a 100-mm-thick lead shield.

The well detector was calibrated, for a range of sample sizes, with ^{237}Pu standardized relative to the injected quantity and dispersed in solution or ash as appropriate. The scintillation counter was calibrated for hepatic activity, with the aid of such a solution dispersed in gelatin contained in plastic bags occupying the liver cavity of a model thorax (Griffith et al. 1979).

RESULTS AND DISCUSSION

Concentrations of plutonium in blood

The data are given in Fig. 1 and Table 2; the results after 14 d suffer from very poor counting statistics. The levels are expressed as the percentage of the injected tracer present in circulating blood. For these purposes, each subject's blood volume, expressed in liters, was assumed to be 7.8% of his body weight expressed in kilograms (Hobbs 1967). The pattern for each subject is similar.

Also shown in Fig. 1 is the mean pattern deduced by Durbin (1972) from data for five of Langham's patients (Hp-1, Hp-5, Hp-6, Hp-8, and Hp-9) injected with Pu(IV) citrate, whose blood circulation Durbin judged to be normal. All of the individual plots for these subjects fell below those for our two volunteers, and Durbin's averaged function predicts concentrations about a factor of 2 lower than we found.

Another subgroup in Durbin's analysis comprised five patients with impaired circulation (Hp-2, Hp-3, Hp-4, Hp-7, and Hp-10); these tended to maintain higher concentrations than patients without this condition, but only in two cases (Hp-4 and Hp-10) did they consistently approach or attain the levels found in our subjects.

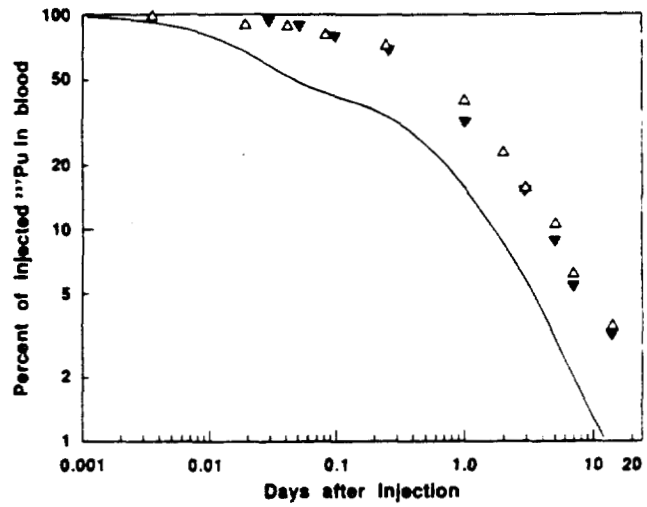

Fig. 1. Measured levels of ^{237}Pu in blood, adjusted for radioactive decay to the time of injection and expressed as the percentage of injected activity present in the subject's estimated total blood volume. △ = Subject A (blood volume = 6.8 L); ▼ = Subject B (blood volume = 4.5 L); ---- Function proposed by Durbin (1972).

Table 2. Content of ^{237}Pu in blood[a].

Subject A		Subject B	
Time (d)	Content (%)	Time (d)	Content (%)
0.0035	99.1 ± 3.1		
0.019	90.3 ± 3.2	0.029	92.3 ± 2.6
0.041	89.3 ± 3.8	0.051	87.8 ± 3.0
0.082	81.6 ± 3.3	0.097	78.2 ± 3.5
0.25	73.0 ± 2.2	0.26	67.8 ± 1.7
1.0	40.4 ± 1.8	1.0	31.5 ± 1.3
2.0	23.2 ± 1.6		
3.0	15.8 ± 1.7	3.0	15.0 ± 1.0
5.1	10.7 ± 1.7	5.1	8.7 ± 1.3
7.0	6.2 ± 1.7	7.0	5.3 ± 1.1
14	3.5 ± 1.4	14	3.1 ± 0.9
21	2.0 ± 1.4	21	0.9 ± 0.9

[a] Percent of injected tracer in estimated total blood volume ± 1σ uncertainty from counting statistics.

Urinary excretion

Urinary excretion of the tracer (Table 3) was very similar for the two subjects, both in the total output up to 21 d (2.4% and 2.0%, respectively) and in the temporal pattern during that period (Fig. 2). Fig. 2 also shows two continuous functions. The upper curve was derived by integration of a five-component exponential function proposed by Durbin (1972) to represent the

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Table 3. Urinary excretion of ^{237}Pu.

Sample number	Subject A End time[a] (d)	Subject A Volume (L)	Subject A ^{237}Pu content[b] (%)	Subject B End time[a] (d)	Subject B Volume (L)	Subject B ^{237}Pu content[b] (%)
1	0.24	0.60	0.702 ± 0.009	0.04	0.18	0.254 ± 0.006
2	0.58	0.70	0.206 ± 0.006	0.25	0.57	0.281 ± 0.006
3	0.86	0.95	0.112 ± 0.005	1.00	0.90	0.270 ± 0.006
4	0.98	0.50	0.048 ± 0.004	2.01	1.46	0.201 ± 0.006
5	2.00	2.20	0.253 ± 0.006	2.99	1.10	0.173 ± 0.006
6	3.00	2.30	0.225 ± 0.006	3.99	0.90	0.096 ± 0.006
7	3.98	1.40	0.120 ± 0.005	5.02	1.00	0.098 ± 0.005
8	4.92	2.25	0.113 ± 0.005	5.99	1.30	0.077 ± 0.005
9	5.77	1.70	0.086 ± 0.005	6.98	1.40	0.071 ± 0.005
10	6.99	1.78	0.078 ± 0.005	7.98	1.35	0.063 ± 0.005
11	7.96	1.87	0.056 ± 0.006	8.98	1.65	0.060 ± 0.005
12	9.06	2.17	0.058 ± 0.006	10.02	1.30	0.036 ± 0.006
13	9.99	1.33	0.050 ± 0.005	11.00	1.70	0.049 ± 0.005
14	10.98	2.77	0.042 ± 0.005	12.00	1.84	0.044 ± 0.005
15	12.00	2.53	0.042 ± 0.005	12.99	0.95	0.039 ± 0.005
16	12.98	1.73	0.040 ± 0.005	13.99	1.43	0.034 ± 0.005
17	13.97	1.94	0.032 ± 0.005	15.00	1.68	0.021 ± 0.008
18	14.95	2.40	0.022 ± 0.006	16.00	1.25	0.027 ± 0.010
19	15.93	1.74	0.022 ± 0.006	17.00	1.43	0.029 ± 0.010
20	17.03	1.70	0.027 ± 0.005	18.00	1.16	0.032 ± 0.007
21	17.84	2.13	0.026 ± 0.007	19.00	1.17	0.031 ± 0.010
22	18.41	2.00	0.015 ± 0.005	20.00	1.92	0.019 ± 0.010
23	19.25	1.63	0.025 ± 0.006	21.00	1.20	0.019 ± 0.008
24	19.95	1.78	0.019 ± 0.006			
25	20.99	2.94	0.016 ± 0.007			
26	21.92	1.28	0.009 ± 0.008			
27	22.92	1.77	0.025 ± 0.007			

[a] Days after injection. Start time for Sample 1 was time of injection; for later samples start time was end time for previous sample.
[b] Percentage of injected quantity, adjusted for radioactive decay between times of injection and measurement; uncertainties are standard errors from counting statistics.

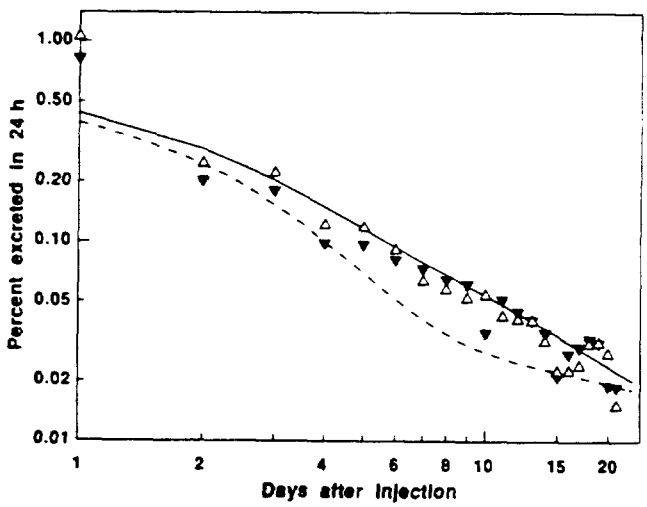

Fig. 2. Urinary excretion, adjusted for radioactive decay and shown as percentages of the administered ^{237}Pu excreted in successive 24-h time periods starting at the time of injection. △ = Subject A; ▼ = Subject B; ---- Prediction of function adopted in ICRP Publication 54 (1988) from Durbin (1972); ---- Prediction of function proposed by Jones (1985).

urinary excretion rate of systemic plutonium in healthy subjects. It was based on her selection of Langham's patients whose renal and hematopoietic functions were assumed to be normal. Durbin's function has been adopted by the ICRP (1988) as a basis for assessing intakes of plutonium from excreted activity, and the integrated form of the function is seen to provide a good overall fit to the data for our subjects. The lower function in Fig. 2 is derived from that formulated by Jones (1985) in an independent treatment of data from Langham et al. (1980) and other sources; it gives a poorer fit to our results.

Renal clearance

The time-integrated concentrations of ^{237}Pu in blood during the first 6 h were determined graphically from Fig. 1. Comparison with the urinary excretion determined during this time period led to estimates of the renal clearance rate (whole blood) of 0.24 L d^{-1} in Subject A and 0.12 L d^{-1} in Subject B. The same comparisons for 1–7 d gave corresponding values of 0.067 and 0.044 L d^{-1}, respectively, and the results for 7–14 d were very similar. The elevated clearances evident in the early stages reinforce inferences by Durbin (1972) for the one subject of Langham et al. (1980)

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Table 4. Fecal excretion of ^{237}Pu.

Sample number	Subject A Voiding time[a] (d)	Subject A Weight (g)	Subject A ^{237}Pu content[b] (%)	Subject B Voiding time[a] (d)	Subject B Weight (g)	Subject B ^{237}Pu content[b] (%)
1	0.59	165	0.001 ± 0.005	0.91	192	0.282 ± 0.007
2	1.45	222	0.116 ± 0.006	1.91	115	0.281 ± 0.006
3	2.51	88	0.216 ± 0.006	2.90	158	0.366 ± 0.007
4	3.54	83	0.210 ± 0.006	3.94	120	0.244 ± 0.006
5	4.55	138	0.244 ± 0.007	4.89	227	0.230 ± 0.007
6	5.44	248	0.331 ± 0.008	5.89	110	0.123 ± 0.006
7	6.23	280	0.276 ± 0.006	6.88	160	0.145 ± 0.006
8	7.42	118	0.094 ± 0.006	7.87	180	0.130 ± 0.006
9	7.62	270	0.129 ± 0.007	8.89	118	0.110 ± 0.006
10	8.60	20	0.015 ± 0.005	9.89	40	0.039 ± 0.005
11	9.54	113	0.060 ± 0.006	10.89	33	0.039 ± 0.005
12	10.40	166	0.077 ± 0.006	11.86	180	0.140 ± 0.007
13	11.58	198	0.122 ± 0.007	12.88	182	0.119 ± 0.007
14	12.50	246	0.111 ± 0.007	13.87	135	0.076 ± 0.006
15	13.59	134	0.059 ± 0.006	14.87	163	0.056 ± 0.007
16	14.52	184	0.055 ± 0.007	15.87	54	0.028 ± 0.006
17	15.45	213	0.057 ± 0.008	16.85	207	0.066 ± 0.055
18	16.67	108	0.032 ± 0.006	17.85	86	0.040 ± 0.006
19	17.50	171	0.048 ± 0.007	18.87	245	0.050 ± 0.007
20	18.54	161	0.043 ± 0.007	19.85	83	0.024 ± 0.006
21	20.20	282	0.031 ± 0.005	20.89	131	0.025 ± 0.007
22	21.37	208	0.042 ± 0.008	21.87	104	0.017 ± 0.007
23	22.43	47	0.019 ± 0.006	22.85	157	0.024 ± 0.008

[a] Time after injection.
[b] Percentage of injected quantity, adjusted for radioactive decay between times of injection and measurement; uncertainties are standard errors from counting statistics.

whose voidings were analyzed individually; however, we were unable to confirm Durbin's report of a minimum in the renal clearance rate after about 1 d.

Fecal excretion

In general, the subjects voided feces once daily during the collection period (Table 4), at times that seldom coincided with the end of each 24-h collection of urine (Table 3). Cumulative fecal excretion plots were produced, with the incremented percentages of the injected tracer plotted at the times of successive voidings. The fecal loss in each 24-h period was assessed by linear interpolation between successive points on these cumulative plots, and the derived excretion rates are shown in Fig. 3. As with the urinary excretion, the two subjects behaved quite similarly, both in their total elimination over 21 d (2.3% for Subject A and 2.6% for Subject B) and in the rate at which the excretion declined with time.

The ICRP (1988) proposed a continuous function relating systemic intake of plutonium and ensuing fecal excretion. The expression adopted originated from Durbin's (1972) analyses of data for six of Langham's (1980) subjects with normal hepatic and digestive functions. To allow comparison with our data, we have integrated the ICRP's continuous function over successive 24-h periods, and the integrated form, shown as the curve in Fig. 3, agrees well with our findings for Subjects A and B at times later than 3–4 d. The earlier discrepancies seen in Fig. 3 presumably arise because the ICRP function evidently does not allow for transit time in the gut.

Uptake by liver

In Fig. 4, we show, for Subject B, the response attributable to ^{237}Pu recorded by the scintillation counter viewing the liver, i.e., the count rate in the photon energy range 23–130 keV, after allowance for contributions from whole-body ^{40}K and radiocesium (the latter mainly from the Chernobyl reactor) and for radioactive decay of the tracer. These count rates increased from about 1,200 counts min^{-1} at 30 min after injection, and again at 100 min, to a mean of 3,309 ± 140 (SD) counts min^{-1} on the five occasions between 43 and 153 d.

The count rates plotted in Fig. 4 would arise from three sources:

1) ^{237}Pu incorporated in the liver;
2) ^{237}Pu in blood within the liver and adjacent tissues; and
3) ^{237}Pu in other tissues within the field of view.

In the early stages, most of the response would arise from source (2). At 30 min, 90% of the injected tracer was estimated to be in blood (Fig. 1) and, if we assume the hepatic uptake at that time to have been negligible, the contributions from (2) at later times may be estimated from the response at 30 min and from the data of Fig. 1. The residual count rates, adjusted for

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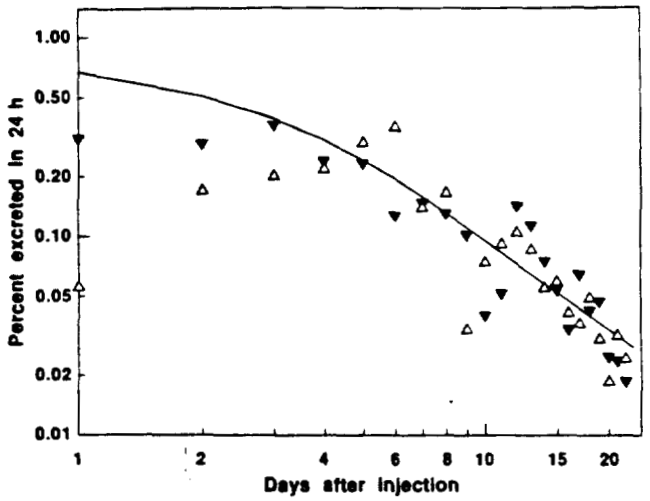

Fig. 3. Fecal excretion, adjusted for radioactive decay and shown as percentages of the administered ^{237}Pu excreted in successive 24-h time periods starting at the time of injection. △ = Subject A; ▼ = Subject B; ---- Prediction of function adopted in ICRP Publication 54 (1988) from Durbin (1972).

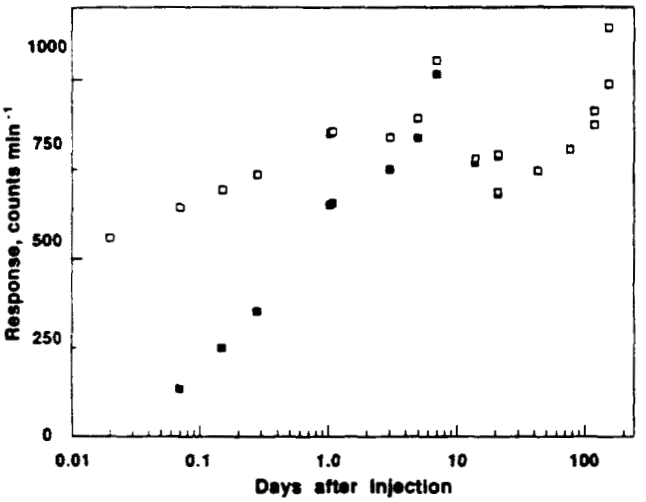

Fig. 5. Response of scintillation counter viewing Subject B's sacrum (counts min^{-1} attributable to ^{237}Pu in range 23–130 keV, with adjustment for radioactive decay). □ = Observed response; ■ = Response after subtraction of estimated interference (negligible after 20 d) from ^{237}Pu in blood.

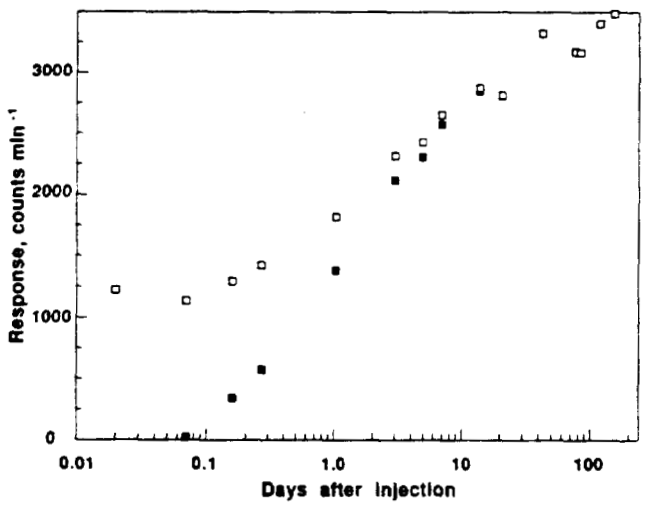

Fig. 4. Response of scintillation counter viewing Subject B's liver (counts min^{-1} attributable to ^{237}Pu in range 23–130 keV, with adjustment for radioactive decay). □ = Observed response; ■ = Response after subtraction of estimated interference (negligible after 20 d) from ^{237}Pu in blood.

this estimated interference from (2), are included in Fig. 4.

Interference from (3) would arise from deposits in bone and in extra-hepatic soft tissue (EHST). Contributions from skeletal tracer can be neglected since a relatively low response was recorded when the same detector viewed regions containing much more bone (Fig. 5). There would be some effect in Fig. 4 from deposits in EHST, but it too is likely to be small. Durbin's report (1972) suggests that in the first few days, the total amount of plutonium in EHST could match that deposited in liver, with by far the largest component being in muscle. However, such an anatomically well-dispersed deposit would not be detected efficiently. We estimate that a 16% residual EHST content after 40 d, as suggested by Durbin's treatment, would contribute no more than 200 counts min^{-1} to the observed 3,300 counts min^{-1} at that time, and we have neglected this component.

The calibration factor for hepatic ^{237}Pu, assessed with the phantom thorax, was 3.5 counts min^{-1} Bq^{-1}; on that basis, Subject B's liver accumulated 68 ± 13% of the injected tracer after 40 d, where the quoted uncertainty arises in the calibration procedure. It is unclear whether this represents the maximum uptake, since an upward trend is maintained up to 153 d. However, at these late times, about 25% of the observed response arose from normal sources of body radioactivity. Errors in estimating this component would be compounded in the correction for radioactive decay; consequently, the significance of this trend is doubtful. The data for Subject A were similar to those in Fig. 4, except that the adjusted response showed no increase between 21 d and the final measurement at 78 d. The level of this plateau indicated a liver deposit of 55 ± 11%.

Uptake by skeleton

Fig. 5 shows the response due to ^{237}Pu when the scintillation counter was located close to Subject B's sacrum. The response from the other bony regions investigated (skull and knees) was much lower, and only in the early stages was it readily distinguished from that due to the usual sources of body radioactivity.

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Allowances for the contributions from ^{237}Pu in blood were made as in the assessment of hepatic uptake. The adjusted plot (included in Fig. 5) suggests that skeletal uptake in Subject B was essentially complete by 3 d; in Subject A, this was delayed until 10–20 d. Additional interference was possible, in the data of Fig. 5, from ^{237}Pu deposited in the liver, but we have no means of quantifying this.

Fig. 5 gives only the temporal *pattern* of uptake at one skeletal site. The count rates cannot be translated into estimates of total skeletal uptake. Aside from difficulties in calibrating the detector to assess the local concentration of tracer in the sacrum, there is no reliable basis for extrapolation to the skeleton as a whole. We can only reach rough estimates by inference, as follows.

In Subject B, the liver content at 21 d was about 60%, and cumulative excretion at that time was 4.6%, i.e., 35 ± 12% was located elsewhere (the uncertainty arising in the calibration for hepatic ^{237}Pu). Possibly no more than one-half of this was skeletal, if Durbin's typical estimate of 17% in EHST at this stage applied. For Subject A at 21 d, the same approach gives 40 ± 11% in bone and EHST combined.

CONCLUSIONS

This experiment has established ^{237}Pu as a useful tracer in studies of the short-term metabolism of plutonium in humans. For future studies, ^{237}Pu with lower levels of alpha-emitting impurities has become available through our collaboration with the Joint Institute for Nuclear Research, Dubna, Russia, allowing us to administer more of the tracer and to prolong periods of study.

The data in Figs. 2 and 3 support current assumptions about the excretion of plutonium featured in recommended monitoring programs (ICRP 1988), which depend heavily on the functions constructed by Durbin (1972). Results for only two subjects are not a strong base for definitive conclusions. It is nevertheless reassuring that, except perhaps in relation to patterns of blood clearance, our data show nothing to invalidate Durbin's expedient division of Langham's (1980) subjects into groups considered to metabolize plutonium in a normal or abnormal manner.

Our rough estimates of 55% and 68% hepatic uptake in the two subjects are higher than the value of 45% adopted in setting annual limits of intake for plutonium (ICRP 1979, 1986); however, partition between liver and skeleton is acknowledged to vary widely between individuals (ICRP 1986). Our data show that uptake at sites of long-term deposition may not approach completion at least for some days after a systemic input. This is of possible relevance to the urgency of chelation therapy following an accidental intake, depending on the formation of metabolites in pools accessible to the chelate and on their relative affinities for it. There is obvious potential for ^{237}Pu in studies of the effectiveness of therapeutic regimes.

Acknowledgements—The authors are indebted to Subjects A and B for their patience and co-operation, and thank the following colleagues who in other ways contributed to the successful execution of this study: R. Bett, L. Dobson, T. Eldred, G. Green, D. Knight, C. Kang, R. T. Morrison, J. F. Smith, and R. Wiltshire. The project was funded by the UK Department of Energy.

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