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Abstract

Three persons who had been injected with known amounts of plutonium in 1945 to 1947, were hospitalized on a metabolic ward in 1973. All excreta were collected for at least eight days and the samples were analyzed for plutonium. For the two subjects who had been injected intravenously with tetravalent ^{239}Pu as the citrate, the urinary excretion rates were 7.6 and 4.7 pCi/day at approximately 10^4 days after injection; these rates corresponded to 2.52×10^{-3}% and 1.41×10^{-3}% of the injected doses per day respectively. The fecal excretion rates were about 40 per cent of the urinary rates. The third subject received an intramuscular injection of hexavalent ^{238}Pu as the nitrate, in the left leg, which was amputated four days later. Almost 50% of the amount injected was found at the injection site and the urinary excretion rate about 9500 days later was 0.06 pCi/day, corresponding to not less than 1.2×10^{-4}% of the initial systemic burden.

From our results for the two subjects with ^{239}Pu, together with previously published excretion rates shortly after injection, and with some reasonable assumptions we calculated the total excretion in, and hence the retention at, 10^4 days. The observed excretion rates at 10^4 days were approximately an order of magnitude higher than those predicted by Langham's equations for urinary and fecal excretion rates as functions of time, and the estimated total excretion was two to three times higher than the predictions obtained by integrating Langham's equations. The possible role of osteoporosis is discussed briefly.

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Introduction

In the years 1945—1947, 18 seriously ill persons were injected with small amounts of plutonium to provide urgently needed information on the excretion rate of this element when it gained access to the blood. Full details of the cases, with reference to the original reports, may be found in a recent review [1]. In 1973, at the instigation of Dr. Patricia Durbin, the author of that review, and with her assistance, we were able to arrange for the hospitalization on a metabolic ward, of three of the subjects who had survived their original illnesses. All urine and feces were collected for at least eight days and the samples were analyzed for plutonium by the method of isotope dilution alpha spectrometry. The isotopic diluent used was ^{242}Pu. The results have been used to calculate the mean daily urinary and fecal excretion rates at about 10,000 days (27.4 years) post-injection; from our results and the excretion rates immediately after injection, estimates of the total excretion and hence the retention have been derived. The results are compared with the predictions of Langham's equations [2].

Pertinent data on the three subjects and their injections are shown in Table I. In case 40-003, ^{238}Pu was injected into the left gastrocnemius muscle four days before a mid-thigh amputation of the leg. A 69.5-g sample of tissue described as "injection site," contained 46.6% of the injected dose. The difference of 53.4% (0.051 μCi) between the amount injected and the amount found in the "injection site," represents an upper limit for the initial systemic burden. This is because of the possibility that unanalyzed tissue adjacent to the "injection site" may have contained unabsorbed plutonium. One other point should be mentioned in connection with this case: there are no early excretion data.

Results

The detailed results of the analyses have been published in a report from this laboratory [3]. We present here only the mean daily excretion rates, in Table II. The urinary excretion rate for case 40-003 was so low that it was necessary to process the whole of a 24-hour sample and count the activity for about 1 week. Therefore only three samples were analyzed. On the other hand adequate statistical precision could be obtained with quite small (≈10%) aliquots of the urine samples of the other two subjects, with counting times of about 1,000 minutes each. The uncertainties shown in Table II are the standard errors of the mean values, including the effects of biological (day-to-day) variation.

In Table III the results are compared with the predictions of Langham's equations; for this purpose each excretion rate is expressed as a percentage of the injected dose. For case 40-003, the result is a lower limit because of the uncertainty in the systemic burden. For this case, the urinary excretion rate was lower (by a factor of about two) than that predicted by Langham's equation,

$$Y_u = 0.2t^{-0.74}, \qquad (1)$$

where Y_u is the daily urinary excretion in per cent of the injected dose, and t is the time in days since the injection. The urinary excretion rates of the other two subjects were approximately an order of magnitude higher than the prediction of equation (1), while the fecal excretion rates were more than an order of magnitude higher than the prediction of the Langham equation

$$Y_f = 0.63t^{-1.09}, \qquad (2)$$

where Y_f is the daily fecal excretion in per cent of the injected dose and t is the time in days since injection.

Excretion Functions

By combining our results with the early excretion data, we can derive functions which describe the excretion rate over 10^4 days. Integration of these functions gives the total excretion, and hence the retention at 10^4 days. In Figures 1 and 2 all the urinary excretion data are plotted from day 1 onwards for cases 40-009 and 40-012 respectively. (The data for case 40-003 will not be considered further.) In each figure the straight line is a plot of equation (1); the change from a broken to a dotted line at 1,750 days reflects the fact that the equation was validated by data only to that time. The continuous curves drawn through the points are the results of fits of simple functions to the data, by the method of least squares. For case 40-009, the data could be described by the sum of exponential and power functions of time, plus a straight line of positive slope to encompass the more than threefold increase in excretion rate between 1,645 days and 10^4 days. It must be emphasized that the function, which fits the data very well, is intended to be descriptive, not predictive.

For case 40-012 the smooth curve drawn through the data is the result of a least squares fit of the sum of three exponential functions of time. While it provides a reasonable description of the data, its correspondence with the actual excretion rate around 100 days could be in error by as much as a factor of three. However, there would only be a small error in an estimate of the total urinary excretion, obtained by integrating the function with respect to time from 0 to 10^4 days, because most of the excretion takes place after 1000 days. (It should be mentioned that an attempt to fit the data with a function of the same form as that used for case 40-009 was not as successful as the fit with the sum of three exponentials. The χ^2-probabilities were 19% and 44% for the two fits respectively.)

Total Excretion

In order to estimate the total excretion, and hence the retention, of the plutonium in cases 40-009 and 40-012 we must make some assumptions, partly because of the paucity of the data, but also because the fecal/urinary excretion ratio is not constant with time. The assumptions are slightly different for the two cases.

(a) For cases 40-009, the observed mean fecal/urinary excretion ratio in the first 23 days after injection was 0.68:1, while at 10^4 days after injection it was 0.42:1. We therefore calculated the total fecal excretion by applying the first ratio to the total urinary excretion corresponding to the exponential and power function components of the equation describing the urinary excretion rate, and the second ratio to the linear part of the equation.

(b) For case 40-012, the mean fecal/urinary excretion ratio changed from 1.44:1 in the first 22 days to 0.38:1 at 10^4 days. We therefore calculated the total fecal excretion by applying the first ratio to the total urinary excretion corresponding to the first two components of the three-exponential equation describing the urinary excretion rate, and the second ratio to the last component.

With these assumptions we have prepared a "balance sheet" as shown in Table IV. Langham's equations predict a total excretion in 10^4 days of 12.2% of the injected dose; this is half (or less than half) of the estimates in Table IV. The biggest departures from Langham's equations occur after 10 years. Between 10 years and 27.4 years, equations (1) and (2) predict a total excretion of only 2.2% of the injected dose, while our estimates are 16% (40-009) and 12% (40-012).

The retention, R, is obtained by subtracting the estimated total excretion from 100%, and it is 68% for case 40-009 and 77% for case 40-012. From the estimate of R, and the measured excretion rate, $\frac{dR}{dt}$, at 10^4 days, we calculate a coefficient of elimination, $\frac{1}{R} \cdot \frac{dR}{dt}$, for each subject as 1.92% per year (40-009) and 0.92% per year (40-012). The corresponding "biological half-lives" are 36 years and 75 years respectively. These elimination rates are similar to those observed for radium in man at late times after intake [4].

The much higher than predicted excretion rates emphasize the danger of extrapolation of biological retention functions beyond the periods of time for which they have been validated. Hempelmann et al. [5] commented on this in their 27-year followup of Manhattan Project plutonium workers. The urinary excretion rates were used to calculate body contents with the aid of equation (1) in 1953 and again in 1973. The later estimates of the burdens were almost all higher than the earlier estimates usually by factors of two to three, but in some cases as high as a factor of five. Perhaps Langham's equations should not be used to calculate body content at times later than five to ten years after intake.

It is interesting to note that the urinary excretion rates of the three subjects decrease in the same order as do their expected degrees of osteoporosis (white female > white male > black male [6]. A decrease as big as fivefold in our estimate of the initial systemic burden of case 40-003 would not invalidate this conclusion. Whether the conclusion is a significant observation remains to be determined, but if it is, some care would need to be exercised in applying and/or modifying the Langham equation. Thus, different equations might be needed for the calculation of the body content 25 or 30 years after intake at age 25 versus intake at age 50, to allow for the different physiological conditions.

Finally, it should be mentioned that the three subjects are in good health, having regard to their age and original illnesses. No effects attributable to irradiation of the skeleton by alpha particles from plutonium have been observed.

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Table I

Details of the subjects and of the injections

Case number	Literature case no.[a]	Sex	Age 1973	Details of injection			
				Date	Material	μCi	Route
40-003	Cal-3	M	62	Jul. 18, 1947	$^{238}Pu(VI)$ nitrate	0.095[b]	I.M.
40-009	Hp-3	F	77	Nov. 27, 1945	$^{239}Pu(IV)$ citrate	0.301	I.V.
40-012	Hp-6	M	72	Feb. 1, 1946	$^{239}Pu(IV)$ citrate	0.331	I.V.

Notes: (a) See references [1] and [2]

(b) See text

Table II

Measured excretion rates of plutonium by three subjects

Case number	Mean time since injection days	Urinary excretion days	Urinary excretion pCi/day ± 1 S.E.	Fecal excretion days	Fecal excretion pCi/day ± 1 S.E.
40-003	9,474	3	0.060 ± 0.003	No analyses	
40-009	9,934	14	7.60 ± 0.21	6	3.17 ± 0.09
40-012	10,008	8	4.68 ± 0.17	8	1.77 ± 0.03

Table III

Daily excretion at 10^4 days as per cent of injected dose

	Langham	Case 40-003	Case 40-009	Case 40-012
Urine	2.19×10^{-4}	$\geq 1.18 \times 10^{-4}$	2.52×10^{-3}	1.41×10^{-3}
Feces	0.28×10^{-4}	-	1.05×10^{-3}	0.53×10^{-3}
Total	2.47×10^{-4}	-	3.58×10^{-3}	1.95×10^{-3}

Table IV

Excretion and retention of plutonium

(t = 10^4 days)

	% injected dose		
	Case 40-009	Case 40-012	Langham
Urinary excretion	20.9	15.4	7.8
Fecal excretion	11.3	7.3	4.4
Total excretion	32	23	12
Retention	68	77	88

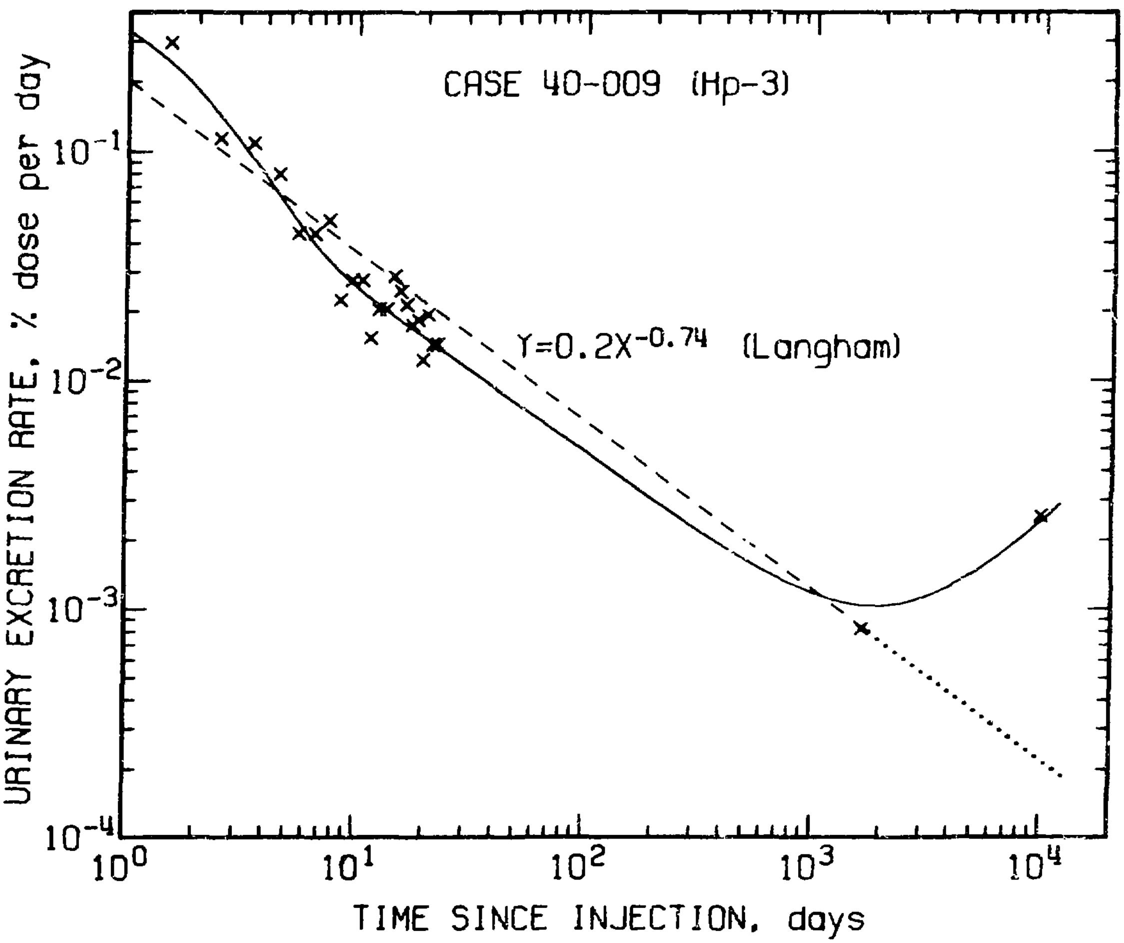

FIG. 1. The daily urinary excretion of ^{239}Pu by case 40-009. The continuous curve is a plot of the equation

$$Y = 0.389 \exp(-0.648t) + 0.127t^{-0.71} + 2.23 \times 10^{-7}t$$

obtained by least squares analysis. Y is the daily urinary excretion in per cent of the injected dose and t is the time in days. The broken straight line represents Langham's equation over the 1,750-day period for which it was validated; the dotted line shows its extrapolation to 10^4 days.

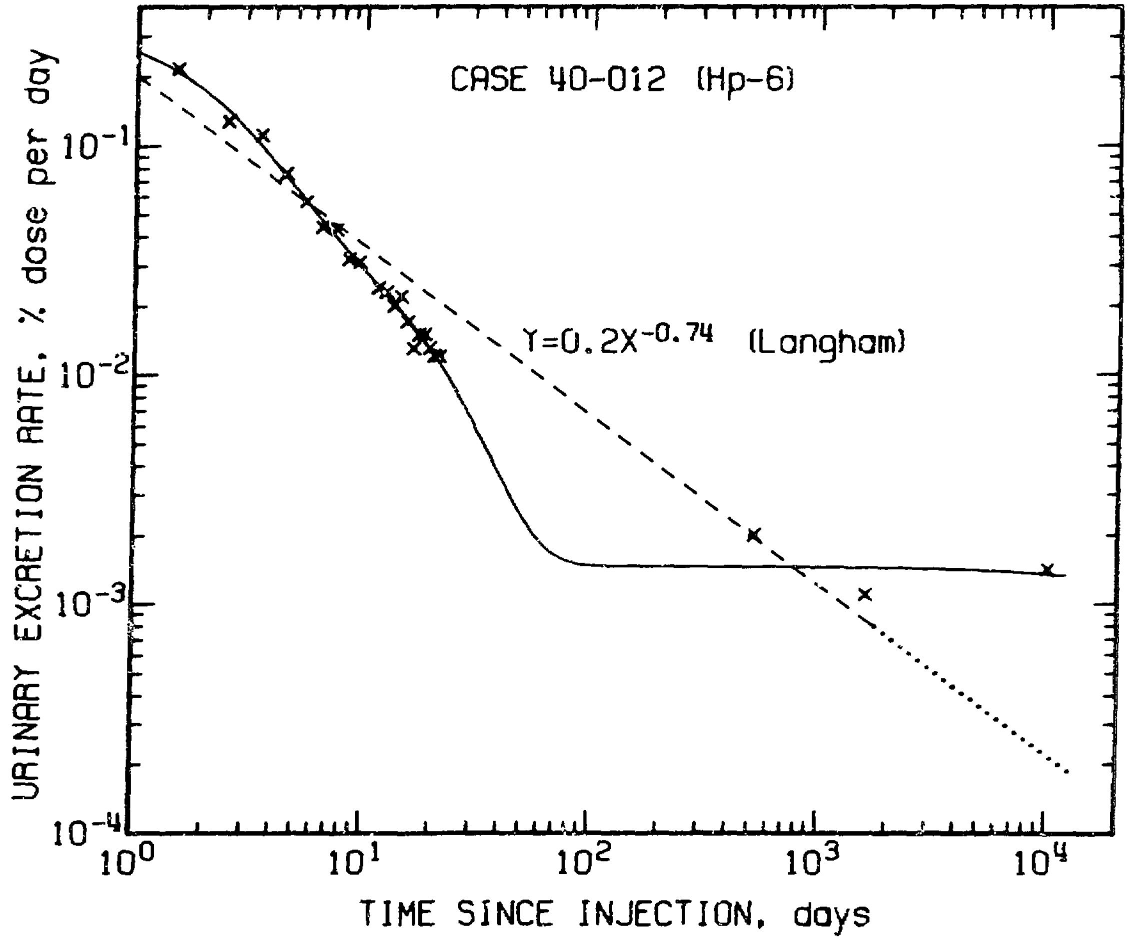

FIG. 2. The daily urinary excretion of ^{239}Pu by case 40-012. The curve through the data is a plot of the equation

$$Y = 0.341 \exp(-0.519t) + 0.0578 \exp(-0.0832t) + 0.00147 \exp(-8.29 \times 10^{-6} t)$$

obtained by least squares analysis. Y and t have the same significance as in Figure 1. Straight line as for Figure 1.