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Center for Human Radiobiology

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FOREWORD

The reader's attention is directed to a preliminary report by J. H. Marshall and P. G. Groer on a model for the induction of bone cancer by alpha radiation. The remarkable ability of this model to fit the observed data on bone malignancies, not only for the human radium cases but for animal toxicity studies as well, is indicative of the power of this approach.

As was the case in our previous Annual Report (ANL-75-3, Part II), exposure data for persons whose body burdens of radium have been measured are given in Appendix A at the back of this report, and the tumor cases considered to be radium-induced malignancies are listed in Appendix B. It should be noted that the average skeletal dose (rads) in Appendix A are calculated to the date of death or to the end of the current year for persons still living. In Appendix B, the rad doses are calculated to the date of diagnosis if prior to death, and may thus be different from the doses given in the other Appendix. For example, the dose to diagnosis of bone sarcoma in 1957 for Case 03-215 was 6860 rads (Table 1, Appendix B), whereas the dose to death in 1971 was 8685 rads (Table 1, Appendix A).

After review of the Plan of the Radium Project that was prepared by CHR staff members in 1974, an ad hoc committee of epidemiologists recommended that the Plan be rewritten to present a general protocol of the Radium Project and specific protocols for limited projects within the total study. This has now been done.

0019254

TABLE OF CONTENTS

Center for Human Radiobiology

Foreword

Theory of the Induction of Bone Cancer by Radiation: A Preliminary Report. I. A Three-Stage Alpha Particle Model and the Data for Radium in Man — 1
J. H. MARSHALL and P. G. GROER

Model for the ^{224}Ra-Protraction Effect — 39
PETER G. GROER and JOHN H. MARSHALL

Differences in the Characteristics of Cell Cultures Established from Seven Human Osteosarcomas — 43
E. L. LLOYD, C. B. HENNING, and F. MACKEVICIUS

Cortical and Trabecular Bone Mineral Mass in the Radius and Ulna — 74
ROBERT A. SCHLENKER and WAYNE W. VONSEGGEN

Thicknesses of the Deposits of Plutonium and Radium at Bone Surfaces in the Beagle — 85
ROBERT A. SCHLENKER and JOHN H. MARSHALL

Bone Surface Concentrations and Dose Rates from ^{239}Pu in a Human Injection Case — 85
ROBERT A. SCHLENKER and BILLIE G. OLTMAN

Plutonium in the Blood of Two Subjects 10^4 Days after Injection — 86
J. RUNDO, R. P. LARSEN, and F. H. ILCEWICZ

The Excretion Rate and Retention of Plutonium 10000 Days after Injection — 89
J. RUNDO, P. STARZYK, R. P. LARSEN, R. D. OLDHAM, J. SEDLET, and J. J. ROBINSON

A Preliminary Report on the Macrodistribution of Radioactivity in the Skeleton of an Individual Who Received Plutonium by Intravenous Injection — 92
R. E. TOOHEY, R. P. LARSEN, and F. H. ILCEWICZ

Progress Report on the Development of the Fission Track Method for the Determination of Plutonium in Biological Materials — 96
R. P. LARSEN and R. D. OLDHAM

0019255

Retention and Excretion of Strontium-90 by a Former Dial Painter 98
R. B. HOLTZMAN, M. ORTMAN, and A. T. KEANE

Calcium in Blood, Plasma, and Red Blood Cells 112
D. R. KUCHTA and J. Y. SHA

An Intralaboratory Comparison of the Measurement of ^{226}Ra in Small Samples of Human Bone 116
D. R. HUFF and J. Y. SHA

Studies of the Reproducibility of Measurements of Radioactivity In Vivo 120
D. R. HUFF, F. MARKUN, and M. A. ESSLING

Revision of Constants used in the Calculation of the ^{226}Ra Content for the CHRIS File VVRA 128
M. A. ESSLING, F. MARKUN, and D. R. HUFF

Measurements of Attenuation Coefficients for Uranium L X Rays in Tissue-Equivalent Absorber 131
R. E. TOOHEY

A Rapid Method for Estimating the Effective Depth of Internally-Deposited ^{241}Am 134
R. E. TOOHEY and J. RUNDO

Radon Monitor for the Vault 137
H. A. MAY and JAMES MIRANDA

Use of a Microprocessor in a Remote Working Level Monitor 146
DONALD J. KEEFE, WILLIAM P. McDOWELL, and PETER G. GROER

Cell-Mediated Immunity in Patients with Osteosarcoma 149
E. L. LLOYD and C. B. HENNING

APPENDIX A. 152

APPENDIX B. 207

Publications 211

0019256

PLUTONIUM IN THE BLOOD OF TWO SUBJECTS 10^4 DAYS AFTER INJECTION

J. Rundo, R. P. Larsen, and F. H. Ilcewicz

The excretory plasma clearance of ^{239}Pu in two subjects 10^4 days after intravenous injection was in the range 0.1 to 0.2 l/day. The plasma concentrations per liter were 0.013% and 0.043% of the retained body contents for the two subjects, respectively.

Two persons who had received 0.3 μCi of plutonium by intravenous injection in 1945 and 1946 were hospitalized on a metabolic ward in 1973. Complete collections of urine and feces were made and blood samples were taken. The results of the urinary and fecal analyses were reported in our previous Annual Report.[1] The results of the blood analyses are reported below. The case numbers identifying the subjects in the early literature[2] are Hp-3 and Hp-6; they have been assigned CHR case numbers 40-009 and 40-012, respectively. The former is a female aged 77 years (in 1973); the latter is a male aged 73 years (in 1973).

The blood samples, which were collected almost exactly 10^4 days after injection, were analyzed for ^{239}Pu by isotope-dilution alpha spectrometry, using ^{242}Pu as the isotopic diluent. The blood had been separated by centrifuging before receipt by us, and the plasma and unwashed red cells were analyzed separately. The ^{239}Pu concentrations in the red cells were lower than those in the plasma samples by factors of 4.2 (case 40-009) and 5.3 (case 40-012). It seems probable that all of the activity found in this fraction was actually in entrained plasma; however, the possibility that some plutonium was associated with the red cells cannot be eliminated. The results for the plasma are presented in column 2 of Table 1.

Values for the urinary and total excretory plasma clearances were calculated from the ratio, excretion rate (pCi/day)/plasma concentration (pCi/liter); values for the mean daily urinary and total excretion rates were taken from our Annual Report.[1] The clearances are given in columns 3 and 4 of Table 1.

Langham et al.[2] measured blood concentrations for these two cases on several occasions during the first 23 days after injection. They expressed

0019257

TABLE 1. Plasma Concentration and Clearance of ^{239}Pu 10^4 Days after Injection

Case No. and sex	Plasma concentration of ^{239}Pu, pCi/liter	Urinary plasma clearance, liter/day	Total excretory plasma clearance, liter/day
40-009 F	97 ± 5	0.078 ± 0.004	0.111 ± 0.006
40-012 M	39 ● 2	0.12 ± 0.01	0.17 ± 0.01

their results as concentrations in whole blood. In order to calculate the early plasma concentrations and clearances, we made three assumptions: (1) the plutonium was all in the plasma, (2) the hematocrit was 40.6 for case 40-009 and 46.2 for case 40-012, and (3) the density of plasma was 1.027 g/cm^3. With these assumptions the urinary plasma clearances were in the range 0.08 to 0.18 l/day for case 40-009 and 0.13 to 0.26 l/day for case 40-012. Total excretory plasma clearances were in the range 0.12 to 0.28 l/day and 0.27 to 0.72 l/day for the two subjects, respectively. In both cases the clearance values increased with time after injection. In case 40-012, they decreased after 10 days, and at 22 days they were essentially the same as at 3 days after injection. In case 40-009 a corresponding decrease had not become apparent by 23 days. The values in Table 1 are similar to those observed just after injection.

It is interesting to note that the plasma clearances in man of plutonium and radium are quite different. The ICRP task group on alkaline earth metabolism[3] adopted a value of 100 l/day for the total excretory plasma clearance of radium. This is almost three orders of magnitude higher than the values in Table 1 for plutonium.

The plasma concentration at 10^4 days, expressed as a percentage of the contemporary body content, was 0.043% per liter for case 40-009 and 0.014% per liter for case 40-012. The higher value for case 40-009 may be the consequence of an expected higher degree of osteoporosis in a woman.

0019258

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THE EXCRETION RATE AND RETENTION OF PLUTONIUM 10000 DAYS AFTER INJECTION*

J. Rundo, P. Starzyk, R. P. Larsen, R. D. Oldham, J. Sedlet,[†] and J. J. Robinson[†]

The majority of long-term studies of the excretion of plutonium by man involve persons who acquired their burden under accident conditions in the laboratory. Even when the route of intake is well defined, the systemic burden can only be estimated within rather wide limits. In this paper we report the results of measurements of the late excretion of plutonium by three persons (one white female, one white male, and one black male) who had received known amounts by injection in the years 1945–1947. Although they had then been considered to have a life expectancy of 5 to 10 years, they survived their original illnesses, at least until 1973 when the present study was undertaken. Full details of the cases, their illnesses, and the injections, together with a re-analysis of the data, have appeared in a recent review.[(1)]

Subjects Hp-3 (female) and Hp-6 received intravenous injections of 0.301 μCi and 0.331 μCi, respectively, of tetravalent ^{239}Pu as the citrate. Subject Cal-3, a black male, received an intramuscular injection of 0.095 μCi of hexavalent ^{238}Pu, as the nitrate, in the left gastrocnemius muscle, four days before a midthigh amputation of the leg. Residual plutonium at the injection site amounted to 46.6% of the injected dose, but there was some uncertainty. The value of 0.051 μCi (53.4%) thus represents an upper limit for the initial systemic burden.

The subjects were hospitalized on a metabolic ward, and all urine and feces were collected for at least eight days. The samples were analyzed for plutonium by the method of alpha spectrometric isotope dilution. The results have been used to calculate the mean daily urinary and fecal excretion rates at

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*Synopsis of a paper submitted to the IAEA Seminar on Diagnosis and Treatment of Incorporated Radionuclides to be held in Vienna, 8–12 December, 1975

[†]Occupational Health and Safety Division.

0019260

about 10000 days post injection. Figure 1 shows all the available data on the daily urinary excretion for Hp-3. The smooth curve through the early points represent the sum of two exponential components, fitted by least squares analysis. The straight line is a representation of Langham's equation.[2] The change from a broken to a dotted line at 1750 days reflects the fact that the equation was only validated to that time.

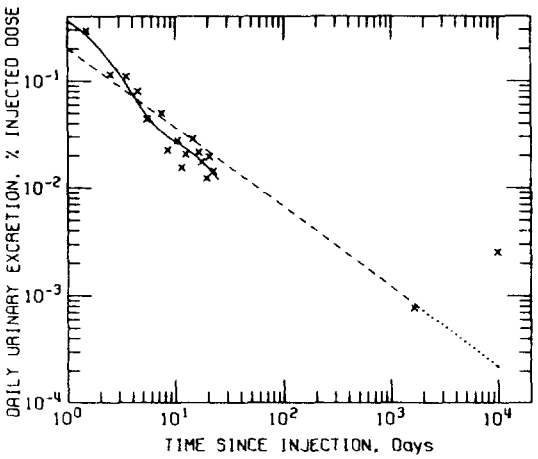

FIG. 1.--Daily urinary excretion of ^{239}Pu by case Hp-3. See text for explanation of curves

The mean daily excretion rates expressed as percentages of the injected doses, are summarized in Table 1. For Hp-3 and Hp-6 the excretion rates are about an order of magnitude higher than predicted by Langham's equations, whereas the urinary excretion rate for case Cal-3 is about a factor of two lower. It may be noteworthy that the three urinary excretion rates decrease in the same order as do their expected degrees of osteoporosis (white female > white male > black male).

From our results and the excretion rates immediately after injection, and with some reasonable assumptions, we calculated the total excretion and retention in the form of a "balance sheet" for cases Hp-3 and Hp-6 (there are no early excretion data in the literature for case Cal-3), and this is shown in Table 2. The assumptions made were such as to be likely to underestimate the long-term excretion, rather than the reverse.

TABLE 1. Mean Daily ^{239}Pu Excretion Rates Expressed as Percent of Dose

	Langham[2]	Case Hp-3	Case Hp-6	Case Cal-3
Urinary:	2.19×10^{-4}	2.52×10^{-3}	1.41×10^{-3}	$\geq 1.18 \times 10^{-4}$
Fecal:	0.28×10^{-4}	1.05×10^{-3}	0.53×10^{-3}	No analyses
Total:	2.47×10^{-4}	3.58×10^{-3}	1.95×10^{-3}	—

TABLE 2. Total Excretion and Retention of Injected ^{239}Pu Expressed as Percent of Injected Dose

	Case Hp-3	Case Hp-6
Urinary excretion		
Short-lived components	1.85	1.35
Long-lived components	15.05	14.14
Fecal excretion		
Short-lived components	1.26	1.95
Long-lived component	6.23	5.20
Total excretion in 10^4 days	24	23
Retention at 10^4 days	76	77

Integration of Langham's equations predicts a total excretion in 10^4 days of 12.2% of the injected dose; this is only half the above estimates.

The coefficients of elimination were calculated from the estimated retention values and the observed excretion rates, as 1.73% per year (Hp-3) and 0.91% per year (Hp-6); these correspond to biological half-lives of 40 years and 76 years, respectively. Apparently some care should be exercised in the use of Langham's equations to calculate systemic burdens of plutonium at very long times after intake.

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A PRELIMINARY REPORT ON THE MACRODISTRIBUTION OF RADIOACTIVITY IN THE SKELETON OF AN INDIVIDUAL WHO RECEIVED PLUTONIUM BY INTRAVENOUS INJECTION

R. E. Toohey, R. P. Larsen, and F. H. Ilcewicz

The concentration of plutonium has been determined in several bone samples from the skeleton of an individual who had received this element by intravenous injection in 1945. The analyses were based on measurements of uranium L x rays with a large xenon-filled proportional counter. The results have been confirmed by radiochemical analysis. The presence of ^{241}Am in the samples has been established. The plutonium content of the skeleton estimated from these measurements is consistent with the values obtained from measurements of the microdistributions on bone surfaces.

Radioactivity measurements were made of the skeletal remains of a woman who in 1945, at age 18, received by intravenous injection 0.3 μCi of plutonium (IV) citrate. At the time of injection she was suffering from Cushing's syndrome, hypertension, nephropathy with uremia, and osteoporosis; she succumbed to her illnesses in 1947. This case, referred to as HP-4 in the early literature,[1] is now designated CHR #40-010.

A preliminary survey of plutonium deposition in the skeleton was made using a large xenon-filled proportional counter to measure the uranium L x rays emitted in the plutonium decay. The feasibility of this approach was established from a measurement made on the right side of the skull. The spectrum obtained is shown in Fig. 1. The prominent peaks at 13.6, 17.2, and 20.2 keV are the uranium x rays which follow the α decay of plutonium, while the lines at 26.3 and 60 keV are γ rays emitted by ^{241}Am. (The 30-keV line is an x-ray escape peak.)

In order to determine the plutonium and americium contents of selected bone samples, the samples were dry-ashed at 600° C in a muffle furnace, and 1.00 g of ash was dissolved in 25 ml of 2 M nitric acid. The solution was transferred to a plastic petri dish (8.89-cm diameter and 1.27-cm depth), and this dish was covered, sealed, and placed inside a polyethylene bag. If the weight of ash from a particular sample was less than 1.00 g, sufficient reagent-grade calcium phosphate was added to the nitric acid to bring the weight of

calcium phosphate in solution to this figure.

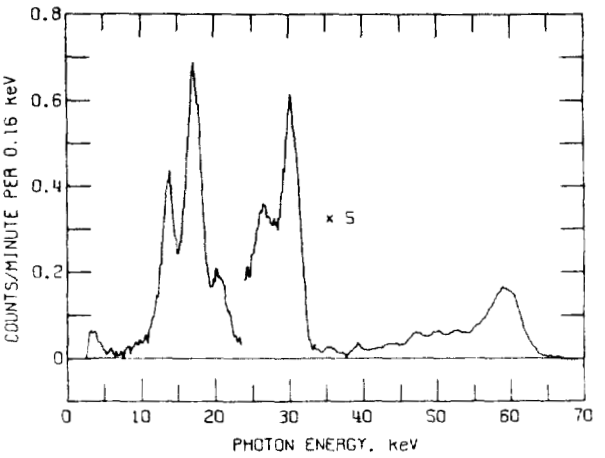

FIG. 1.--The x- and γ-ray spectrum from the skull of case 40-010. The spectrum has been smoothed over five-channel intervals, and the counts in the ^{241}Am region (25–60 keV) have been multiplied by five for clarity.

To perform the measurements the proportional counter was inverted, and the dishes were placed directly on the beryllium window. Counting times were of the order of 10^4 min. Background measurements were made using dishes containing the same amount of 2 M nitric acid and 1.00 g of inactive calcium phosphate. The counting system was calibrated by measurements of the radiation from nitric acid solutions of calcium phosphate containing known amounts of isotopically pure (> 99.9%) ^{239}Pu and ^{241}Am.

The spectra obtained from the samples were fitted with spectra from the standards by the method of least squares with the program GASP.[2] The spectrum of 8.1 counts/min observed from a sample prepared from a portion of first lumbar vertebra and the fitted spectrum computed by the program are shown in Fig. 2. The amounts of plutonium and ^{241}Am found in each sample are given in Table 1.

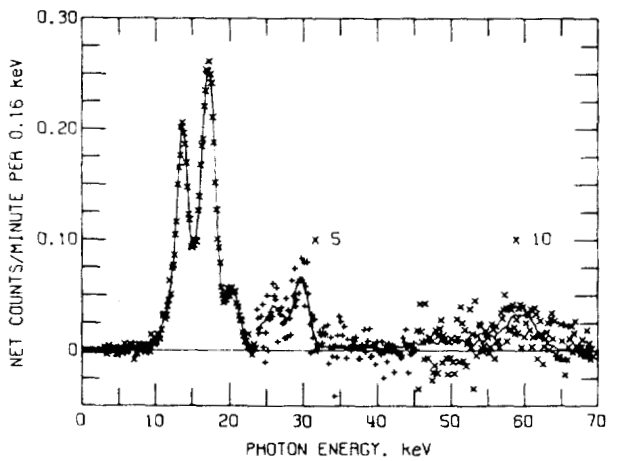

FIG. 2.--The x- and γ-ray spectrum of one gram of bone ash from the first lumbar vertebra dissolved in 2 M HNO_3. The solid line is a fitted spectrum of ^{239}Pu and ^{241}Am standards computed by GASP.

0019264

TABLE 1. The Concentrations of Pu and ^{241}Am in Bone Samples of Case 40-010

Sample Number	Site	^{239,240}Pu dpm/g ash		^{241}Am dpm/ ash	Pu/Am activity ratio
		Prop. Counter	Radiochem.	Prop. Counter	Prop. Counter
R41	First lumbar vertebra	1694 ± 51	1813	38 ± 5	45 ± 6
K41	Femur head	264 ± 33	304	5 ± 4	52 ± 43
E01	Humerus head	221 ± 34	338	9 ± 4	25 ± 12
E02	Humerus midshaft	40 ± 10	55	not detectable	
E61	Innominate	1124 ± 45	1395	28 ± 4	40 ± 6
E63	Innominate	1218 ± 43	1217	26 ± 4	47 ± 7

The presence of ^{241}Am in the samples indicated that the plutonium used for the injection was not pure ^{239}Pu but contained other isotopes of plutonium. To verify this, plutonium was separated from a urine sample from another individual who had been injected with plutonium from the same source,[1] and it was analyzed mass spectrometrically. The isotopic composition obtained was ^{239}Pu, 98.34%, ^{240}Pu, 1.66 ± 0.08%, and ^{241}Pu, 0.01 ± 0.005%. Thus, the amount of ^{241}Am present in the samples is consistent with its all having grown in from ^{241}Pu. The weighted mean of the five estimates of the ^{239,240}Pu-to-^{241}Am alpha-activity ratios as obtained by proportional counting is 42 ± 3; the value calculated from the mass spectrometric measurement is 64 ± 42. In addition, a small amount of ^{238}Pu was found by radiochemical measurements.

Since the calibration source was isotopically pure ^{239}Pu, it was necessary to correct the ^{239}Pu x-ray activity fitted by GASP for the contribution from ^{240}Pu. The x-ray/alpha-particle yields of ^{239}Pu, ^{240}Pu, and ^{241}Am are 0.046, 0.115, and 0.376, respectively. Consequently, for the mass ratios given above, 78% of the x-ray activity was due to ^{239}Pu, 12% to ^{240}Pu, and 10% to ^{241}Am. The small x-ray contributions from ^{241}Pu and ^{238}Pu were neglected.

There are large variations in the concentrations of Pu in the bone samples — as much as a factor of 7.7 for different bones which are predominantly trabecular. Only one sample of purely cortical bone (humerus midshaft) was analyzed, and its plutonium concentration was much lower than that of the

0019265

other samples. A very approximate calculation involving several major assumptions as to the total skeletal mass and the pattern of deposition gives a value for the total skeletal content of 30 to 50% of the amount injected. These results are consistent with those obtained by neutron-induced autoradiography.[3]

The total plutonium content of the skeleton, the concentration in each bone, and the distribution in selected bones are being established by radiochemical analysis. The results of radiochemical analysis for plutonium of those bone samples which were analyzed using the proportional counter are also given in Table 1. A radiochemical method has been developed for determining the ^{241}Am concentration of bone. Selected bones will be analyzed for both radionuclides, and a comparison of the ^{239,240}Pu-to-^{241}Am activity ratios will be made to establish whether or not selective leaching of either element has occurred in the 26 years between burial and exhumation.

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0019266