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Polonium Metabolism in Adult Female Baboons

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The biokinetics of polonium in nonhuman primates (*Papio anubis*) has been studied after intravenous injection of ^{210}Po citrate. The urinary excretion of polonium in the baboon could be described by a single exponential function with a half-time of 15.6 days. Excretion fractions of polonium were found to be markedly different from those reported for other species, including humans. Polonium-210 was found to be distributed throughout the soft tissues of the baboon with 29% of the injected polonium being deposited in liver, 7% in kidneys and 0.6% in spleen. Retention of polonium in all tissues exhibited single exponential functions; however, the biological half-times were variable, ranging from 15 to 50 days.

INTRODUCTION

Polonium-210 (^{210}Po) is a naturally occurring α-particle emitter (radiological half-life, 138.4 days) in the ^{238}U decay chain which can also be produced anthropogenically by irradiating stable bismuth with neutrons and allowing the resulting ^{210}Bi to decay. Humans are constantly exposed to polonium isotopes due to the natural formation and fallout of radon progeny, which include ^{218}Po, ^{214}Po and ^{210}Po. In the 1940s and 1950s, workers were exposed to ^{210}Po while performing chemical separation of ^{210}Po from neutron-irradiated ingots of bismuth. This work was a major part of the United States government's Manhattan District Project, whereby ^{210}Po in association with beryllium was used as a neutron source to trigger the fission reaction in the detonation of the atomic bomb (*1*).

Polonium-210 translocates from primary deposition sites into the circulatory system and is then redistributed throughout the soft tissues of the body. Information about the metabolism of polonium obtained from studies of its biokinetics in animals, although useful for establishing radiological protection guidelines, was determined to be equivocal here for defining the systemic dose to workers from urine bioassay data obtained previously. Therefore, a study of the excretion, retention and distribution of ^{210}Po in nonhuman primates was made.

The studies of the biokinetics of polonium in nonhuman primates were carried out using baboons (*Papio anubis*) exposed as a result of intravenous administration. Previous studies demonstrated that the parameters of the biokinetics of polonium differed when soluble solutions (e.g., polonium citrate) were used compared to studies when colloidal solutions (e.g., neutralized polonium chloride) were used (*2–4*). The chemical form of polonium used in this study was ^{210}Po citrate.

The criteria for selection of a physicochemical form of polonium for use in these studies were as follows: (1) a chemical matrix which would keep polonium in a stable, "soluble" form to emulate the diffusible state of polonium across biological membranes; (2) a chemical matrix which would be compatible with and nontoxic to blood constituents; (3) a solution pH which was comparable to that used in previous studies of injected polonium; (4) a solution which was ultrafilterable (0.22 μ*M*) to ensure a pyrogen- and colloidal-free medium; and (5) a solution which was reproducible and relatively easy to prepare. The citrate form we employed met the specified criteria best and represents, to as great a degree as possible, the form of polonium that would pass through a biological membrane after deposition in the lungs or gastrointestinal tract.

PROCEDURE

Six adult female baboons were administered ^{210}Po citrate via single injections into the femoral vein. Preparation of the injection solution is described in Appendix A.

The administered doses were chosen to be nontoxic both chemically and radiologically, i.e., so as to be indicative of "normal" metabolism during study periods of 1, 7, 14, 30, 80 and 91 days. The 30- and 91-day study animals (B30d and B91d) were injected with approximately 37 Bq/kg (compared with the 7.4–11.1 Bq/kg doses injected into the other baboons) so as to permit radiochemical determinations of ^{210}Po in excre-

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TABLE I
Injection Data and Identification of Baboons Used in the Study of Polonium Metabolism

Baboon	Body weight (kg)	Dose (Bq kg^{-1})	Duration of study (days)
B1d	10.1	9.62	1
B7d	11.0	8.88	7
B14d	16.6	8.14	14
B30d	13.0	29.6	30
B91d	13.0	28.9	91
B80d	16.5	5.55	80

ta samples and tissues at times as great as 90 days after exposure. The injection solution parameters are summarized in Table I.

During all phases of this study, baboons were maintained at the New York University Medical Center's Laboratory for Experimental Medicine and Surgery in Primates (LEMSIP). Urine and fecal samples were collected daily (urine only from the 80-day study animal, B80d). Urine samples were acidified with 1*N* HCl. Feces samples were dried prior to analysis.

With the exception of B80d, all of the baboons were euthanized to determine the distribution and biokinetics of the polonium. Baboons were sacrificed at 1 day, 1 week, 2 weeks, 1 month and 3 months after exposure. All sacrifices were carried out by exsanguination after the intravenous administration of anesthesia.

Polonium has been shown to associate with proteinaceous material in the blood, with the majority of the blood-borne nuclide resident in red cells bound to hemoglobin (*5*). To maximize the accuracy of tissue ^{210}Po measurements, the residual blood ^{210}Po content was subtracted from each sample result (which included ^{210}Po from both the tissue mass and its residual blood volume). This was accomplished by labeling the blood with ^{51}Cr prior to sacrifice after the procedure described in Appendix B (*6*), gamma-counting each tissue sample to determine residual blood volume, and subtracting the product of the residual blood volume and the blood ^{210}Po concentration from the measurement of ^{210}Po in the tissue sample.

Analyses of ^{210}Po in all major organs were performed in addition to measurements of polonium in skeletal and muscle samples. The entire skeleton of B30d was analyzed radiochemically as were aliquots of muscle samples taken from various areas of the body. The total skeletal ^{210}Po burdens of the other four animals were calculated based on extrapolations of the activity measured in the right femur; the total muscle ^{210}Po burdens were calculated by multiplying the average concentration of two or three samples taken from different areas of the body by the entire muscle mass (which was measured). The radiochemical procedures used for the analyses of ^{210}Po in excreta, blood and tissue samples are given in Appendix C.

All data describing excretion and distribution of ^{210}Po in baboons have been adjusted for radioactive decay and consequently represent biological mechanisms only.

RESULTS

Urinary and fecal excretion of polonium by the baboon can be characterized by single exponential kinetics through 90 days. Figures 1a and 2a show that polonium was excreted by the baboon with biological half-times of 15.6 ± 1.5 days for urine and 14.4 ± 2.5 days for feces as determined using non-linear least-squares regression analysis. Figures 1b and 2b describe polonium excretion by the baboon as a function of polonium concentration (i.e., activity of ^{210}Po per gram urine or feces), rather than the daily output. The biological half-time estimate is reduced for both pathways, to 12.4 ± 2.2 and 13.6 ± 0.8 days for urine and feces, respectively. At 90 days

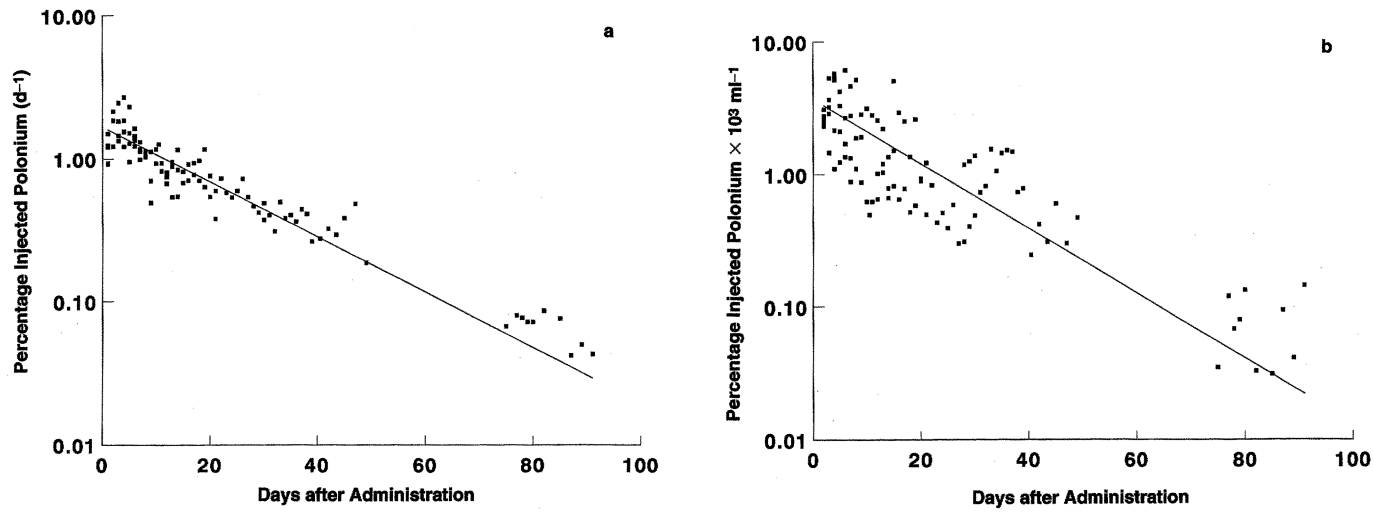


FIG. 1. Excretion of ^{210}Po in urine expressed as daily output, $Y = 1.7 \times e^{-[(0.693/15.6) \times t]}$ (panel a) and as ^{210}Po concentration, $Y = 3.7 \times e^{-[(0.693/12.4) \times t]}$ (panel b).

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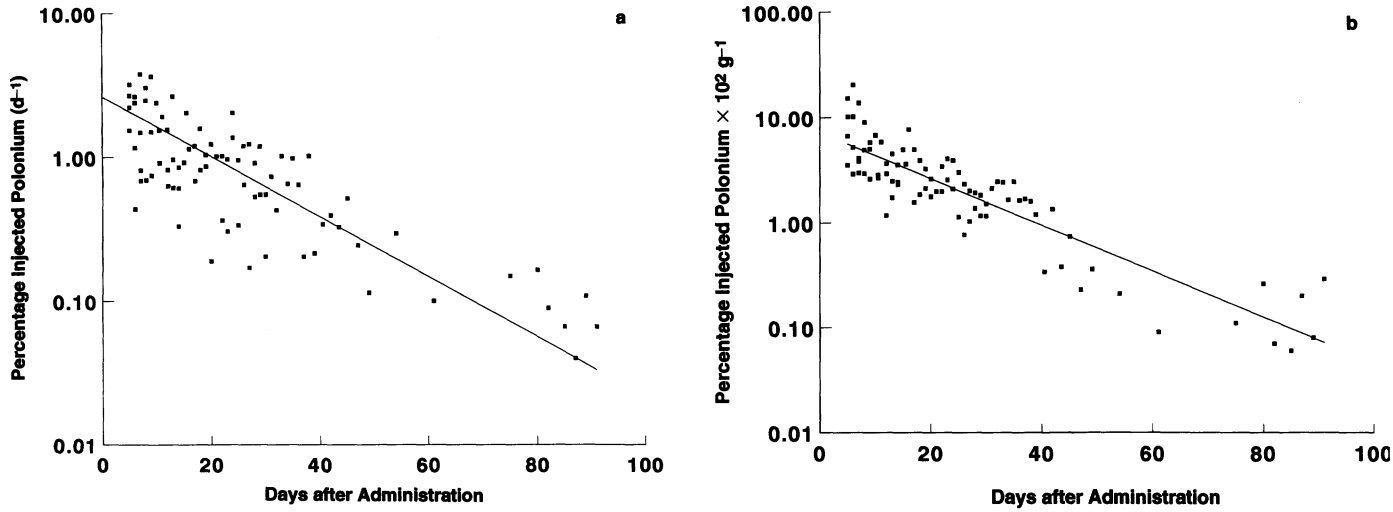


FIG. 2. Excretion of ^{210}Po in feces expressed as daily output, $Y = 2.6 \times e^{-[(0.693/14.4) \times t]}$ (panel a) and as ^{210}Po concentration, $Y = 7.2 \times e^{-[(0.693/13.6) \times t]}$ (panel b).

after injection, however, the daily urinary polonium elimination constant[1] is estimated to be 0.004 days^{-1} (corresponding to a 160-day biological half-time), indicating a possible secondary, slower phase of polonium elimination.[2] Regression analysis of the data for feces does not include polonium recovered during the first 4 days after injection due to the extreme variability observed in the output of polonium during this initial period. All of the baboons (with the exception of B91d) eliminated a large quantity of the administered activity (12–14%) in feces on day 2, 3 or 4 of the experiment.

Cumulative urinary excretion accounts for 37.7 ± 4.0% of the injected activity. Total fecal excretion of polonium is 55.1 ± 11.2% of the injected polonium, resulting in a feces-to-urine ratio of 1.5 ± 0.3. Table II presents a summary of excretion parameters found for baboons after intravenous administration of polonium.

An examination of the data for blood and feces from the baboon sacrificed at 91 days after injection suggests that as much as half of the ^{210}Po in the syringe was inadvertently injected into the femoral muscle. For example, at 10 min after injection, the blood from each of the other exposed animals contained 50 to 70% of the injected polonium. On the other hand, the polonium in the blood of B91d accounted for only 37.8% of the injected activity at that time. To a lesser degree the 7-day study animal (B7d), with 52.9% of the injected polonium present in the blood at 10 min, and the 1-day study animal (B1d), with 50.0% of the injected polonium present at 10 min, may also have received some intramuscular administration accidentally. Measurements of the retention of polonium in the blood of B91d indicate that, for the first week, the levels of polonium did not decline significantly after the completion of an initial rapid phase. The level of polonium in the blood was relatively constant from day 2 (14.8% of the injected polonium) to day 14 (11.9% of the injected polonium). It could be that the slower than expected clearance of the polonium from the blood was due to a slow and constant absorption of ^{210}Po from the muscle into the blood.

The excretion pattern of ^{210}Po in feces during the first few days after injection of B91d also supports the possibility of a combination of intravenous and intramuscular administration. An immediate and precipitous drop in the content of polonium in feces was observed to follow the peak output of polonium in feces during days 2 through 4 for the three other baboons. The output of ^{210}Po in the feces of B91d followed a different pattern during the first week. A large (12 to 14%) daily maximum excretion was not observed in the feces of that animal, as was the case for both B7d and B30d. Rather, levels ranging from 1.1 to 3.8% of the injected polonium were found in fecal samples collected from days 2 through 8 after injection, with levels increasing daily from day 4 through day 7 after injection. Continued input of polonium into the bloodstream during the first few days (presumably from a muscle deposit) might account for the observed pattern of excretion in feces during this period.

Due to the possibility that B91d was exposed via both the intravenous and intramuscular routes, its data for polonium excretion were compared to the data from the other baboons by an analysis of covariance. The relatively large single-day maxima observed in the feces of the other baboons were not used in the analysis. For the data for both the urinary and fecal excretion, there were no statistically significant differ-

[1]Daily urinary elimination constant, λ, estimated: $\lambda = A_t/BB_t$ where A_t = daily quantity of polonium eliminated prior to sacrifice and BB_t = body burden at time of sacrifice.

[2]Additional data beyond 91 days are needed to provide conclusive evidence of a secondary phase in urinary excretion.

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TABLE II
Observed Excretion of Polonium

Matrix	Study period (days)	Biological half-time (days ± SE)	Excretion fraction (± SE)
Urine	91	15.6 ± 1.5	0.38 ± 0.04
Feces	91	14.4 ± 2.5	0.55 ± 0.11

ences found between either the slopes (i.e., biological half-times) or the intercepts of the single exponential excretion functions ($P > 0.05$) for B91d and all other study animals combined. Therefore, the excretion data for all study animals were combined for the determination of the polonium urinary and fecal excretion functions.

Figures 3 and 4 show the retention of ^{210}Po citrate in the blood of baboons. The levels of polonium in the blood of B7d and the 14-day study animal (B14d) fell to 10.8 ± 2.6% of the injected activity during an initial rapid phase having a biological half-time of 38.7 ± 6.0 min. A second longer retention period followed with a half-time of 8.4 ± 3.1 days. Rapid-phase kinetics was not determined for the other animals because no blood was collected during the first day after exposure. The second retention component for polonium in B30d appeared to be the same as that of B7d and B14d, i.e., with a half-time of 12.5 ± 2.7 days. However, twice as much of the injected polonium (21.7 ± 1.3%) was still present in the blood at the onset of the second phase.

The data for ^{210}Po retention in the blood of B91d are separated graphically into plasma and red blood cell content for the samples taken through day 21. After completion of the initial rapid-phase retention, the fraction of activity in the red cells exceeds that in plasma by a factor of 5.5. The second phase of polonium retention commences with 16.6 ± 0.5% of the injected activity remaining in the circulatory system. The combined loss of ^{210}Po from the plasma and red cells of B91d is consistent with the retention half-time of 19.1 ± 2.5 days observed in aliquots of total blood. This half-time is almost twice as long as that exhibited for the retention of polonium in the blood of the other baboons.

Measurable levels of polonium were recovered in all tissues assayed; however, distribution was not uniform throughout the soft tissues. The distribution of ^{210}Po observed in baboon tissues is provided in Table III. Kidney and liver tissue accumulated the highest fractions of systemically deposited ^{210}Po, with concentrations greater than 0.1% of the injected activity per gram wet weight during the first week after injection. The concentration of ^{210}Po in the spleen was approximately one-third that observed in the kidney and liver. The lung, adrenal gland and pancreas had ^{210}Po concentrations approximately one-tenth that of kidney and liver.

Data describing residual blood measurements in baboon tissues are summarized in Tables IV, V and VI. Table IV provides the blood concentration of ^{51}Cr and the measurement of total blood volume. Table V provides several tissue weights and the concentration of residual blood within those tissues after exsanguination as determined from ^{51}Cr measurements. Table VI provides the contribution of blood-borne polonium to tissue polonium burdens for a number of tissues. Much of the ^{210}Po measured in bone marrow samples was due to blood-borne polonium. The ^{210}Po content of the lungs and spleen was reduced by approximately 25% at 1 day after injection. The contributions of blood-borne polonium in other tissues, such as the liver and kidneys, were not as significant as that observed for the spleen and lung.

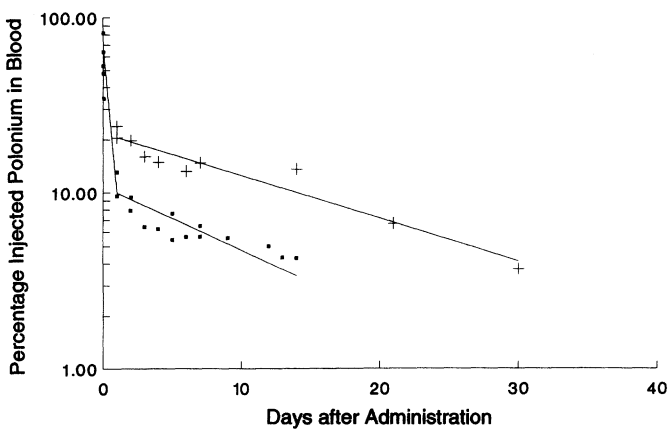


FIG. 3. Retention of ^{210}Po in whole blood from baboons B7d and B14d (including the initial rapid phase), $Y = 63.2 \times e^{-[(0.693/0.027) \times t]} + 10.8 \times e^{-[(0.693/8.4) \times t]}$ (lower curve) and from baboon B30d, $Y = 2.17 \times e^{-[(0.693/12.5) \times t]}$ (upper curve).

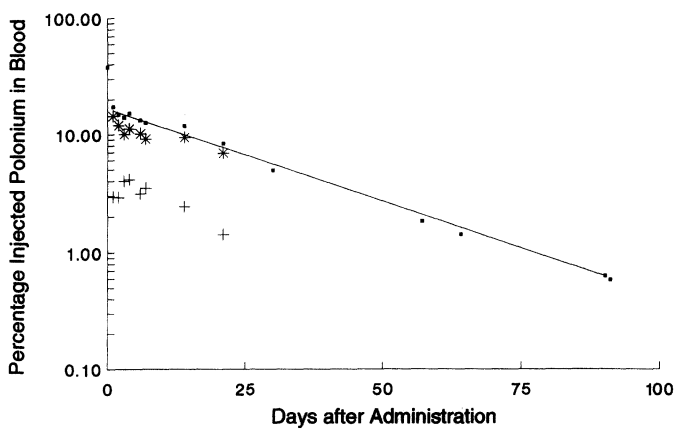


FIG. 4. Retention of ^{210}Po in the whole blood (■), $Y = 16.6 \times e^{-[(0.693/19.1) \times t]}$, and data for red blood cells (*) and plasma (+) of baboon B91d.

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TABLE III
Polonium Content in Organs and Tissues

Tissue \ Baboon no. / Days in study	B1d 1	B7d 7	B14d 14	B30d 30	B91d 91
			Percentage injected polonium tissue^{-1}[a]		
Blood	20.5	5.6	4.3	3.7	0.59
Liver	33.2	19.3	15.3	6.3	0.48
Kidney	7.2	4.4	4.8	4.3	0.57
Spleen	0.95	0.40	0.39	0.24	0.05
Lung	1.8	0.78	0.42	0.75	0.22
Ovary	0.03	0.03	0.01	0.04	0.01
Thyroid	0.09	0.01	0.003	0.01	0.002
Adrenal gland	0.10	0.02	0.03	—	0.004
Pancreas	0.30	0.24	0.17	0.20	0.02
Brain	0.06	0.29	—	0.55	0.28
GI tract[b]	18.8	8.3[c]	5.1[c]	4.6[c]	0.7[c]
Muscle[d]	6.6	8.2	6.4	8.7	1.0
Skeleton[e]	4.8	5.3	4.8	4.1	1.0
Pelt[d]	5.2	6.6	6.9	—	5.6
			Percentage injected polonium g^{-1}		
Blood	0.027	0.007	0.004	0.004	0.0008
Liver	0.105	0.105	0.059	0.026	0.003
Kidney	0.129	0.103	0.082	0.083	0.014
Spleen	0.035	0.025	0.018	0.021	0.003
Lung	0.015	0.009	0.006	0.008	0.002
Ovary	0.011	0.015	0.005	0.008	0.003
Thyroid	0.073	0.008	0.004	0.003	0.002
Adrenal gland	0.039	0.011	0.010	—	0.001
Pancreas	0.018	0.018	0.008	0.011	0.001
Brain	0.0005	0.002	—	0.003	0.002
GI tract	—	—	—	—	—
Muscle[d]	0.002	0.002	0.0007	0.001	0.0002
Skeleton[e]	0.002	0.002	0.002	0.002	0.0003
Pelt[d]	0.005	0.005	0.003	—	0.004

[a] 2–10% relative range of errors.
[b] Sum of stomach, small and large intestines (with contents).
[c] Large intestine ^{210}Po content was estimated.
[d] Mean of three samples.
[e] Entire skeleton of B30d was analyzed. Other values estimated. Right femur of B30d constituted 3.29% of the skeletal ^{210}Po burden. Skeletal ^{210}Po = right femur ^{210}Po content/0.0329.

The retention of polonium in systemic tissues can be described best by single exponential kinetics. The curves for baboon tissues are shown in Figs. 5–8. Partitioning (i.e., the fraction of the administered polonium initially deposited in a tissue) and retention half-times for autopsied tissues are provided in Table VII. Loss of ^{210}Po from the liver proceeded more rapidly than from all other tissues, with a half-time of 15.4 ± 0.6 days. The half-times for kidney, spleen, pancreas and skeleton ranged from 25 to 35 days, whereas lungs, ovaries and thyroid exhibited retention half-times of 45 to 50 days. The percentage of administered polonium in pelt ranged from 5 to 7% throughout the study period. It decreased from 6.9 on day 14 to 5.6 on day 91, which may have indicated a secondary slower phase of polonium retention with an approximate half-time of 300 days.

The change in the tissue distribution of ^{210}Po with time due to different loss rates among the various tissues noted by Stannard (*7*) was also observed in the baboon. Table VIII provides the ^{210}Po content of each organ or tissue. The changes in the relative distribution of ^{210}Po (on the basis of weight) with time are compared for some tissues in Fig. 9. The spleen retained a relatively constant fraction of the total body content. The relative amount of polonium body content found in the pelt underwent a dramatic increase, climbing from 5% at day 1 to greater than 50% of the content at day 91. A similar increasing trend was also observed, although to a lesser extent, in the ovaries and brain. The kidney underwent a relative increase in polonium content during the initial 30 days after injection and then decreased between days 30 and 91. On the basis of wet weight, the relative concentration of polonium in muscle tissue

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TABLE IV
Total Blood Volume and ^{51}Cr Blood Labeling Data

Baboon	Body weight (kg)	^{51}Cr blood concentration (kBq ml^{-1} ± SD)	Total blood volume (ml ± SD)
B1d	10.1	0.59 ± 0.10	749.8 ± 45.5
B7d	11.0	3.96 ± 0.42	785.1 ± 29.1
B14d	16.6	0.70 ± 0.06	1162[a]
B30d	13.0	1.98 ± 0.02	970.1 ± 6.4
B91d	13.0	6.06 ± 0.62	782.1 ± 32.4

[a]Volume estimated to be 7% of body weight; majority of the activity in the syringe did not enter bloodstream.

was constant through the first 30 days. The fraction of the body content present in the blood first decreased and then remained relatively constant through day 30.

Data analysis included careful examination of excretion relative to injected quantities of polonium. Approximately all of the injected polonium was recovered in the baboon excreta, blood and tissue samples. Table IX lists the material balance of the injected polonium at the time of sacrifice.

DISCUSSION

Injection Solution

Differences in the biokinetics of polonium may be expected based on the physicochemical form of the injection solution used. In the current study, polonium citrate was chosen since it is relatively free of colloids upon administration and as such is compatible with biological use (*2*).

The distribution of the nuclide will be influenced immediately by the scavenging function of the tissues of the reticuloendothelial system, which have been shown to contain larger concentrations of colloidal polonium than noncolloidal polonium after intravenous administration. This may also be reflected in a more rapid initial loss of colloidal polonium from the blood, as indicated by the half-time of less than 40 s observed after injection of colloidal polonium in rats (*3*). In contrast, the initial-phase half-time of 39 min in the current study is comparable to the 25 min half-time in rats injected with soluble polonium solutions (*3*).

Studies in which polonium was administered by gavage have demonstrated that both colloidal and noncolloidal polonium will be absorbed through the gastrointestinal tract (*8, 9*). In cats, the acidic environment in the stomach caused ^{210}Po aggregates to break up and become available for absorption to the same extent as soluble ^{210}Po citrate. Ionic or soluble complexes of polonium are most likely the principal forms absorbed from the gastrointestinal tract (*8, 9*). The chemical form of the polonium isotope played a minor role in its tissue distribution and excretion rate. Indeed, it was noted that there were only minor differences between the mean tissue distribution and urinary excretion values after single intravenous administrations of colloidal and noncolloidal polonium, although the study had a duration of only 7–10 h (*8*).

Excretion

The baboon excreted a total of 38% of the injected polonium via urine with a half-time of 15.6 days. These data differed from the parameters of the biokinetics of excretion reported previously for rats. Rats were observed to excrete a total of 5 to

TABLE V
Average Organ Weights and Residual Blood Concentration

Organ	Number of samples	Weight (g ± SD)	Residual blood (ml g^{-1} ± SD)
Liver	5	241.22 ± 46.11	0.10 ± 0.04
Kidneys	5	50.10 ± 8.31	0.11 ± 0.02
Spleen	4	17.08 ± 7.20	0.51 ± 0.19
Lungs	5	94.55 ± 19.74	0.23 ± 0.05
Heart	5	54.42 ± 6.17	0.05 ± 0.02
Brain	4	143.50 ± 19.51	0.01 ± 0.00
Pancreas	5	17.70 ± 2.77	0.03 ± 0.02
Adrenal gland	4	2.68 ± 0.42	0.19 ± 0.11
Muscle	21	5750 ± 2070	0.01 ± 0.00
Bone femur	3	87.48 ± 5.20	0.01 ± 0.01
Bone marrow[a]	19	—	0.06 ± 0.09
Pelt	4	1229.7 ± 92.3	0.01 ± 0.00

[a]The entire bone marrow was not collected. The residual blood concentration was based on measurement of the marrow extracted from the right femur.

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TABLE VI
Residual Blood ^{210}Po Contribution to Various Tissues Using Exsanguination and ^{51}Cr Labeling Technique

Organ	Days after injection	Injected polonium (gross percentage)	Injected polonium (corrected percentage)	Difference (%)
Liver	1	33.9	33.2	2.1
	7	19.4	19.3	0.6
	14	15.4	15.3	1.1
	30	6.4	6.3	1.3
	91	0.5	0.5	2.7
Kidneys	1	7.4	7.2	2.6
	7	4.4	4.4	0.7
	14	4.9	4.8	0.5
	30	4.4	4.3	0.7
	91	0.6	0.6	0.7
Spleen	1	1.2	0.9	23.5
	7	0.5	0.4	16.9
	14	0.4	0.4	11.4
	30	0.3	0.2	13.1
	91	0.05	0.05	10.4
Lungs	1	2.3	1.8	28.6
	7	0.9	0.8	20.9
	14	0.5	0.4	17.3
	30	0.8	0.7	12.2
	91	0.2	0.2	7.3
Heart	1	0.6	0.4	36.0
	7	0.4	0.3	5.4
	14	0.1	0.1	4.1
	30	0.2	0.2	6.6
	91	0.06	0.05	10.0
Bone marrow[a]	1	0.005	0.002	125.4
	7	0.004	0.003	28.4
	14	0.014	0.013	6.3
	30	0.024	0.022	9.0
	91	0.002	0.002	7.0

[a]Bone marrow extracted from right remur. Considerable variation in sample sizes.

10% of systemically incorporated polonium in urine (*7, 10, 11*), which is significantly lower than that observed in this study.

The baboon excreted 55% of the injected polonium in feces with a half-time of 14.4 days. The cumulative feces-to-urine ratio of ^{210}Po of 1.5 ± 0.3 after intravenous administration in the nonhuman primate was markedly different from data reported elsewhere for other animals, including humans. Regression analysis of data generated by studies conducted at the University of Rochester (*10*) estimate a cumulative feces-to-urine ratio of 10 after intravenous administration of poloni-

TABLE VII
Distribution Parameters for Systemic Polonium in Selected Organs of the Baboon

Organ	Partition coefficient ± SE	Biological half-time (days ± SE)	r^2 of the regression
Liver	$2.9 \times 10^{-1} \pm 1 \times 10^{-2}$	15.4 ± 0.6	0.99
Kidneys	$7 \times 10^{-2} \pm 1 \times 10^{-2}$	24.5 ± 3.0	0.95
Spleen	$6 \times 10^{-3} \pm 2 \times 10^{-3}$	24.9 ± 3.0	0.95
Pancreas	$3 \times 10^{-3} \pm 4 \times 10^{-4}$	24.7 ± 2.2	0.95
Adrenal gland	$5 \times 10^{-4} \pm 6 \times 10^{-6}$	25.2 ± 6.3	0.83
Skeleton	$6 \times 10^{-2} \pm 3 \times 10^{-3}$	33.8 ± 2.7	0.97
Lungs	$9 \times 10^{-3} \pm 5 \times 10^{-3}$	44.9 ± 18.0	0.66
Ovaries	$3 \times 10^{-4} \pm 2 \times 10^{-5}$	48.2 ± 22.8	0.61
Thyroid	$7 \times 10^{-5} \pm 6 \times 10^{-6}$	49.5 ± 31.2	0.56

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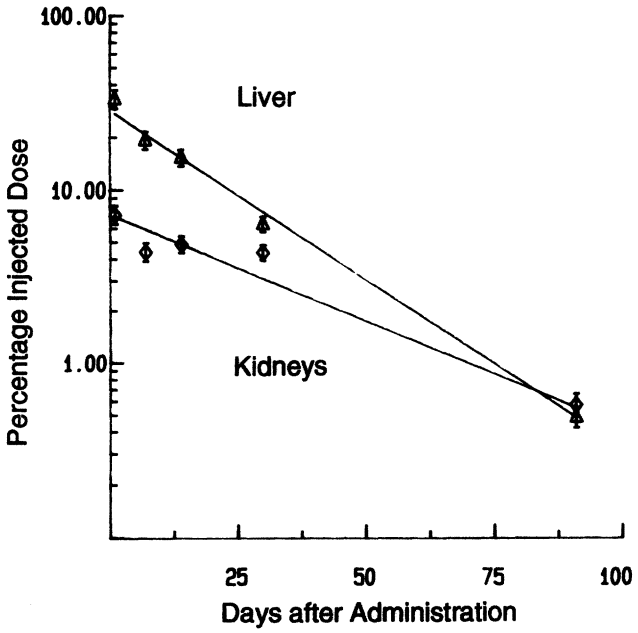


FIG. 5. Retention of ^{210}Po in the liver and kidney after serial sacrifice of five adult female baboons.

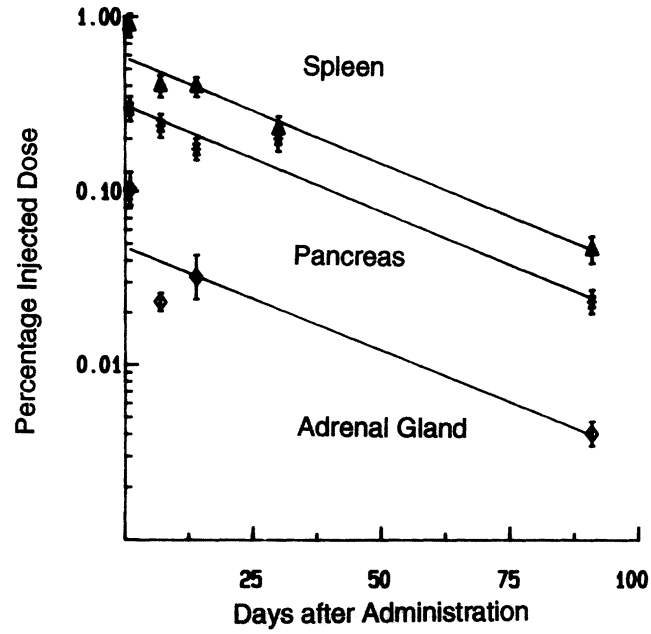


FIG. 6. Retention of ^{210}Po in the spleen, adrenal gland and pancreas after serial sacrifice of five adult female baboons.

um in rats.[3] Evaluation of the polonium recovered in feces from workers exposed occupationally was at least 10 times the ^{210}Po recovered in urine (*12*). However, the observed approximate sixfold differences in human and nonhuman primate feces-to-urine ratios has been explained in recent publications[4] (*13*). Data in these publications indicate that the differences between feces-to-urine ratios for humans and nonhumans may be due to the radiochemical procedures used to analyze the urine samples from humans. That being the case, data in this study suggest that the feces-to-urine ratio for baboons more closely reflects the excretion ratio in the aforementioned human case studies than do data for the rat.

Excretion via both urine and feces proceeded more rapidly in the nonhuman primate than expected when compared to previous studies of metabolism. Most of the data for humans as well as studies of metabolism in other animal species indicate biological excretory half-times ranging from 30 to 50 days for polonium[5,6,7,8] (*10–12, 14, 15*). However, recent studies of the radiochemical procedures used to analyze polonium content in urine indicate an approximate half-time of 20 days for polonium in human urine, which is more rapid than described previously (*13*). This urinary excretion rate for polonium is comparable to the half-time of 15.6 days determined in the baboon.

A previous study of polonium metabolism in rats over long periods (e.g., in excess of 400 days) indicated that the loss of polonium from most tissues demonstrated a slow-phase component (*7*). The data for urinary and fecal excretion of ^{210}Po in the nonhuman primate also suggest the existence of a long-term phase of polonium excretion which could not be characterized adequately during the 91-day study period. At the time of sacrifice, the daily urinary excretion rate of B91d corresponded to a half-time of 160 days. The total ^{210}Po excreted by both routes (which can be predicted from the integrated exponential excretion functions) is 93% of the injected amount for the baboon. Re-evaluation of data for humans presented by Fink (*11*) indicated that 89% of the ^{210}Po administered intravenously was excreted by a human volunteer based on the sum of the integrated single exponential urinary and fecal excretion functions (*13*). A relatively small percentage of polonium excreted with a longer half-time might describe some or all of the 7% (baboon) or 11% (human) of the administered activity not accounted for by the single phase excretion functions.

It is possible that a portion of the body burden is stored in hair. Ladinskaya *et al.* (*16*) reported ^{210}Po concentrations in human hair to be higher than concentrations of ^{210}Po in soft tissue and skeleton in persons exposed solely to environmental levels of the nuclide. The baboon pelt samples maintained a constant 5 to 7% of the injected activity, corresponding to

[3]A. Fellman, Primate polonium metabolic models and their use in estimation of systemic radiation doses from bioassay data. Ph.D. dissertation, New York University Medical Center, 1989.

[4]D. P. Hickman, H. B. Spitz, N. Cohen and A. Fellman, A new model for evaluating internal dose from the intake of polonium-210. UCRL-CR-108132, 1991.

[5]D. H. Naimark, Acute exposure to polonium (medical study of three human cases). Mound Laboratory Report MLM-67, 1948.

[6]D. H. Naimark, Effective half-life of polonium in the human. Mound Laboratory Report MLM-272, 1949.

[7]E. S. Spoerl, A derived biological half-life of polonium in humans. Mound Laboratory Report MLM-626, 1951.

[8]W. E. Sheehan, Effective half-life of polonium. Presented at the 10th Annual Bio-assay and Analytical Chemistry meeting, 1964.

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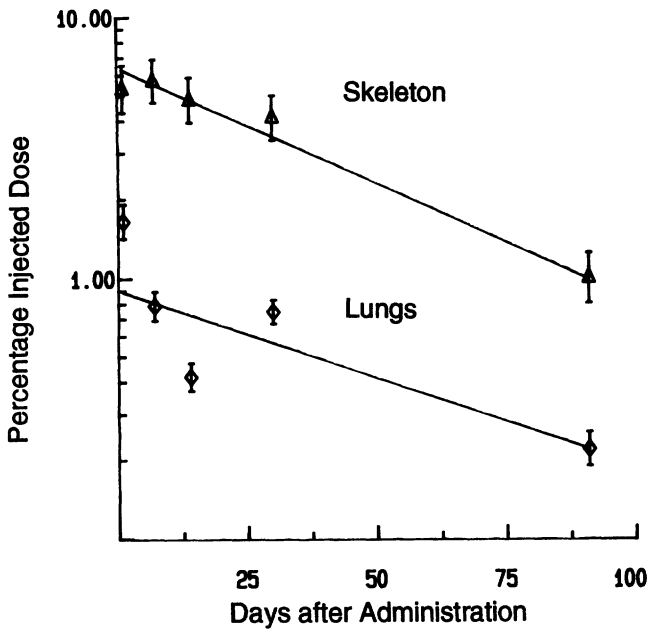


FIG. 7. Retention of ^{210}Po in the lungs and skeleton after serial sacrifice of five adult female baboons.

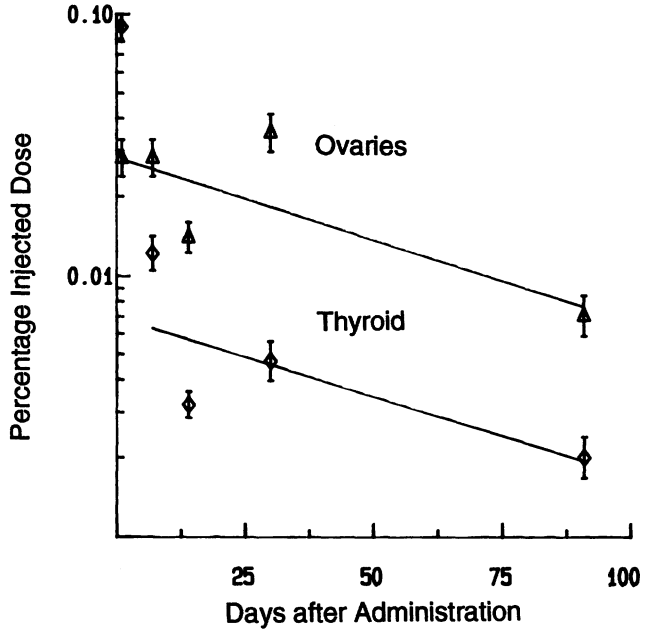


FIG. 8. Retention of ^{210}Po in the thyroid and ovaries after serial sacrifice of five adult female baboons.

5% of the body content on day 1 after injection and 53% of the body content on day 91 after injection. The predominant route of the polonium excreted during a second, long-term phase may be into the pelt of the baboon. This trend was observed in dogs after exposure to polonium by inhalation, as the percentage of body content in the pelt increased steadily from 11% on day 28 to 51% on day 149 after exposure (*17*). The majority of activity was found in the hair follicles. Unfortunately, the baboon samples assayed were not separated into the hair, skin and fat components which comprise the pelt.

Retention in the Blood

The retention of ^{210}Po in the blood exhibited similar kinetics among the five study animals. However, some differences were observed in the percentage of administered activity in blood at the conclusion of the initial rapid phase of polonium retention in the blood. The second, slow phase commenced within a few hours after injection, with approximately 11% of the injected activity in the blood of B7d and B14d, 17% in the blood of B91d, and 22% in the blood of B30d. These data may reflect normal biological variability. Another possibility for the differences observed in the early retention of polonium is the relative amounts of the administered activity which were injected accidentally into the femoral muscle.

The red blood cell-to-plasma ratio of polonium in the baboon of 5.5 was much lower than that reported for some other species. For example, ratios in rats were 22.8 at day 2 after intravenous administration and ranged as high as 41.7 at day 24 after administration (*5*). However, data similar to these observed for the baboon were reported for the rabbit, which had red cell-to-plasma ratios of polonium of 8.5–15.6 during day 1 through day 20 after intravenous administration.

Rabbits and humans were found similar with respect to the percentage of polonium binding to red blood cells (*18*), and apparently the amount of binding to red blood cells in the baboon is comparable to these two species. Based on data reported by Fink (*11*), Stannard and Smith noted that a larger fraction of blood polonium may be in the plasma of humans than in the rat (*18*). This is certainly true in the baboon.

Interestingly, the rabbit is the one animal species studied previously which exhibits parameters of urinary excretion of polonium similar to those of the baboon. Due largely to rapid urinary excretion of the nuclide, rabbits have a whole-body retention half-time of only 20 days, compared to greater than 30 days in the rat (*19*) and approximately 15 days in the baboon. Further, the rabbit excreted 30% of the administered polonium via urine through day 70 after both intravenous and intratracheal administration (*19*), which is similar to the percentage excreted in baboon urine over the same period.

Studies in the rat and rabbit showed that polonium may be bound more tightly to red blood cell constituents (e.g., hemoglobin) than to other materials (*5*). It is possible that the rate and fraction of urinary excretion of polonium are related to the percentage of polonium associated with plasma. The rabbit, nonhuman primate and human show a consistency, i.e., relatively higher fractions of polonium associated with plasma and rapid urinary excretion accounting for a greater percentage of total excretion of the nuclide than seen in other species.

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TABLE VIII
Percentage of Polonium Body Content in Baboon Tissues

Baboon no. / Days in study / Tissue	B1d 1	B7d 7	B14d 14	B30d 30	B91d 91
			Percentage body content tissue^{-1}[a]		
Blood	20.3	9.2	8.7	10.3	5.5
Liver	32.7	31.4	31.0	17.4	4.5
Kidney	7.1	7.1	9.8	12.0	5.3
Spleen	0.9	0.6	0.8	0.6	0.4
Lung	1.8	1.3	0.8	1.2	2.1
Ovary	0.03	0.05	0.03	0.17	0.07
Thyroid	0.09	0.02	0.01	0.01	0.02
Adrenal gland	0.10	0.04	0.06	—	0.04
Pancreas	0.3	0.4	0.4	0.5	0.2
Brain	0.06	0.5	—	1.4	2.6
GI tract[b]	18.5	13.5[c]	10.4[c]	12.7[c]	6.4[c]
Muscle[d]	6.5	13.4	12.8	24.1	9.7
Skeleton[e]	4.7	8.5	8.9	11.4	8.9
Pelt[d]	5.1	10.8	14.1	—	53.0
			Percentage body content g^{-1}		
Blood	0.03	0.01	0.01	0.01	0.007
Liver	0.11	0.17	0.12	0.07	0.02
Kidney	0.13	0.17	0.17	0.23	0.13
Spleen	0.03	0.04	0.04	0.06	0.03
Lung	0.01	0.01	0.01	0.02	0.02
Ovary	0.01	0.02	0.01	0.04	0.03
Thyroid	0.07	0.01	0.01	0.01	0.03
Adrenal gland	0.04	0.02	0.02	—	0.01
Pancreas	0.02	0.03	0.02	0.03	0.01
Brain	0.0005	0.003	—	0.01	0.02
GI tract	—	—	—	—	—
Muscle[d]	0.002	0.003	0.001	0.004	0.001
Skeleton[e]	0.002	0.003	0.003	0.005	0.003
Pelt[d]	0.005	0.008	0.01	—	0.04

[a] 2–10% relative range of errors.
[b] Sum of stomach, small and large intestines (with contents).
[c] Large intestine ^{210}Po content was estimated.
[d] Mean of three samples.
[e] Entire skeleton of B30d was analyzed. Other values estimated. Right femur of B30d constituted 3.29% of the skeletal ^{210}Po burden. Skeletal ^{210}Po = right femur ^{210}Po content/0.0329.

TABLE IX
Material Balance of Injected Polonium

Sacrifice time (days)	B1d (1)	B7d (7)	B14d (14)	B30d (30)	B91d (91)
			Percentage injected polonium (±1 SD)		
Feces	0.4 ± 0.01	26.7[a] ± 0.3	22.4 ± 0.3	41.6 ± 0.2	54[b] ± 0.2
Urine	1.0 ± 0.1	13.3 ± 0.1	17.2 ± 0.1	25.1 ± 0.1	36[b] ± 0.1
Blood	20.5 ± 0.5	5.7 ± 0.1	4.3 ± 0.1	3.7 ± 0.04	0.6 ± 0.02
Soft tissues	63.8 ± 1.2	35.1[c] ± 0.6	27.1[c] ± 0.3	18.6[c] ± 0.1	2.4[c] ± 0.03
Muscle[d]	6.6 ± 0.5	8.2 ± 0.4	6.4 ± 0.2	8.7 ± 0.1	1.0 ± 0.09
Pelt[d]	5.2 ± 0.4	6.6 ± 0.4	6.9 ± 0.2	lost	5.6 ± 0.5
Skeleton[e]	4.8 ± 0.3	5.7 ± 0.3	4.8 ± 0.1	4.1 ± 0.04	1.0 ± 0.06
Total	102 ± 1.4	101 ± 0.9	89 ± 0.6	102 ± 0.4	101 ± 0.6

[a] Day 4 sample was lost. Polonium-210 content was estimated.
[b] Polonium content of some samples from days 60–80 was estimated.
[c] Polonium content of large intestine (and contents) was estimated and ranged from 6% (B7d) to 0.5% (B91d).
[d] Mean of three samples.
[e] Entire skeleton of B30d was analyzed. Other values estimated: Skeletal ^{210}Po = femur ^{210}Po content/0.0329. Right femur of B30d constituted 3.29% of the skeletal ^{210}Po burden.

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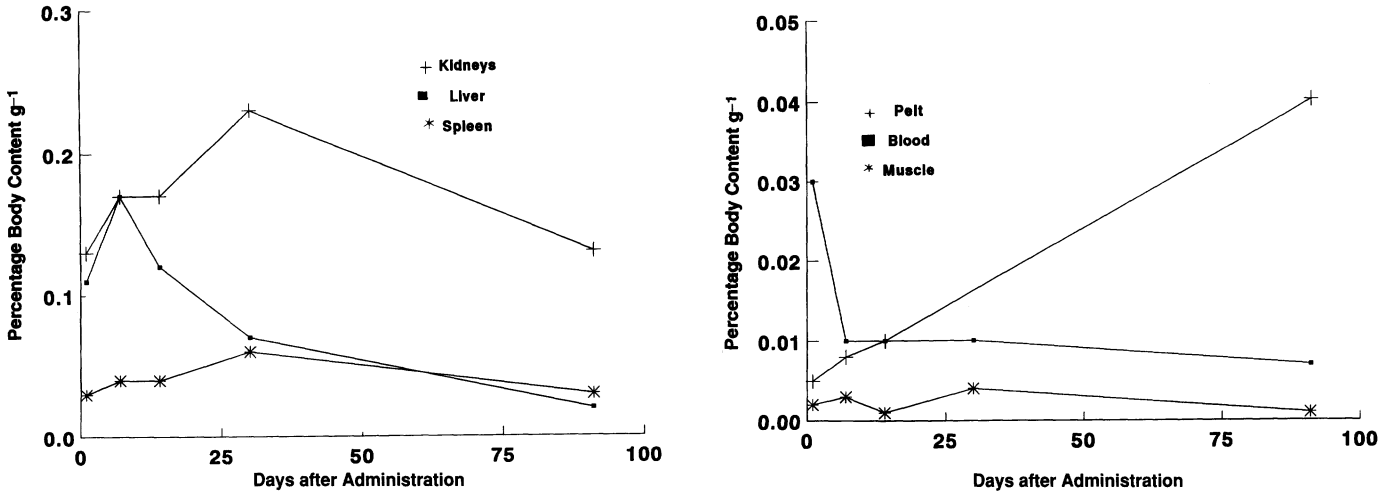


FIG. 9. Relative concentration of ^{210}Po in several tissues after serial sacrifice of five adult female baboons.

Tissue Distribution and Retention

Polonium has often been described as a soft-tissue seeker which is distributed throughout the whole body (*10, 11, 20–22*). For the most part, the data for baboons support this general description of the distribution of ^{210}Po.

The distribution of ^{210}Po among soft tissues in the baboon was generally similar to data reported for other laboratory animals, especially the rat. Liver, kidney and spleen were the tissues with the greatest ^{210}Po concentrations. However, the relative ^{210}Po content in the spleen was much lower in the baboon than in the rat and somewhat lower than in the mouse (*18*). Two factors may have contributed to this difference: (1) The injection solution administered to the baboon was filtered (i.e., free of polonium aggregates) whereas the polonium chloride solutions used in previous studies of metabolism in other species consisted largely of colloidal polonium. The spleen and other tissues of the reticuloendothelial system would be expected to remove aggregates from the bloodstream (2). The data for baboon tissue are "blood-free" measurements. Subtracting the residual blood ^{210}Po from the total activity measured in the spleen resulted in a 25% reduction in that tissue's ^{210}Po content.

The rate of excretion of ^{210}Po in feces is the same as the rate of loss of ^{210}Po from the liver, with half-time estimates of 14.4 ± 2.5 and 15.4 ± 0.6 days, respectively. The kinetics supports the conclusion that the biliary excretion pathway is a primary mechanism for the removal of polonium from the liver. A significant amount of polonium may be removed via the liver/biliary pathway since a total of 55% of the administered activity is excreted in feces.

Retention of ^{210}Po in various baboon tissues exhibited half-times ranging from 15–50 days. In general, the kinetics of tissue retention observed in the baboon was similar to other

TABLE X
Data from Previous Experiments for ^{210}Po Retention in Various Tissues after Intravenous Administration[a]

	Biological half-time (days) Species				
Tissue	Rabbit	Rat	Mouse	ICRP 30	Baboon
Kidney	18	38	43	50	24.5
Liver	11	11	43	50	15.4
Spleen	8	31	18	50	24.9
Lung	8	47	23	—	44.9
Muscle	—	38	42	—	—
Blood	—	56	—	—	8–19[b]
Skeleton	—	23	—	—	33.8
Lymph nodes	—	56	—	—	—
Reference	(*22*)	(*7*)	(*23*)	(*21*)	current study

[a]Adapted from Moroz and Parfenov (*22*).
[b]There was also an initial rapid phase exhibiting a half-time of 38.7 min.

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species studied previously, especially the rat. Data for biological half-times found in previous studies are summarized in Table X. Differences in tissue processing, composition of the injection solution, and dose levels make a more rigorous comparison with previous studies difficult to quantify.

SUMMARY

Internal dosimetry due to the intake of ^{210}Po may be estimated by monitoring excreta and applying a suitable model of metabolism consisting of both excretion and tissue retention parameters (e.g., kinetics and partitioning fractions). The ICRP 30 model for polonium metabolism is based primarily on studies of metabolism in rats and a limited number of cases of excretion after accidental intake by humans (*21*). The current research expands on this limited database by examining, for the first time, the retention and excretion of polonium in a nonhuman primate species.

Excretion of systemic ^{210}Po was found to proceed with a half-time of 15 days, compared to the half-time of 50 days postulated by the ICRP 30 model. Retention half-times among soft tissues ranged from 15–50 days, as predicted from previous studies. The concentration of ^{210}Po in tissues can be broken into three general groups. Tissues of the reticuloendothelial system contain the highest concentrations of ^{210}Po. The ovary, thyroid, adrenal gland and pancreas comprise a group of organs with an intermediate degree of ^{210}Po concentration. The brain, muscle and skeleton are tissues with the lowest concentrations of ^{210}Po. Use of the parameters for metabolism derived from this primate study will enable dosimetrists to estimate tissue-specific effective doses and their relative errors more accurately based on ^{210}Po bioassay data.

APPENDIX A

Preparation of ^{210}Po Citrate Solution for Intravenous Administration to Nonhuman Primates

1. Withdraw 0.5 ml ^{210}Po stock solution (2*N* HCl) into a 1-ml tuberculin syringe.
2. Transfer polonium solution into a preweighed 30-ml plastic bottle and obtain the solution weight.
3. Add 9.5 ml of 0.1 *M* Na citrate solution slowly with mixing (in 0.1-ml aliquots).
4. Reweigh bottle to determine the amount of citrate added.
5. Wait 15–20 min to complete reaction.
6. Draw off an aliquot. Calibrate solution and test pH with short-range indicator paper (solution pH 4–5).
7. Draw up solution into a 35-ml syringe with a Leur-lock neck.
8. Attach a 0.22-μ*M* Swinex (Millipore) filter and collect filtered solution in a preweighed 30-ml plastic bottle. Weigh.
9. Test pH (4–5) with short-range paper and calibrate an aliquot of the solution.
10. Compare solution activity concentrations before and after filtration to determine filterability.
    (Final administration solution is 100% ultrafilterable (0.22 μ*M*) with pH 4–5 and 0.1 *M* Na citrate.)

APPENDIX B

Preparation of ^{51}Cr-Labeled Erythrocytes[9]

1. Draw a 5-ml whole blood sample into a vacutainer containing 0.75 ml of acid citrate dextrose (ACD) solution.
2. Centrifuge at 2000 rpm for 5 min at 4°C.
3. Remove serum and buffy coat.
4. Wash RBCs three times with physiological saline (PS), 0.9% NaCl.
5. Add dropwise 0.37–0.74 kBq of sterile sodium ^{51}Cr per ml RBC with mixing.
6. Incubate mixture with mixing for 30 min at 37°C.
7. Wash ^{51}Cr–RBC with PS.
8. Resuspend in 5–10 ml culture medium (90% RPMI-1640, 10% bovine serum, 1% Penn/Strep.).
9. Refrigerate overnight at 4°C.
10. Centrifuge at 2000 rpm for 5 min.
11. Remove medium and wash ^{51}Cr–RBC with PS.
12. Resuspend ^{51}Cr–RBC in approximately 10 ml PS.
13. Inject (iv) cells.
14. Allow labeled RBC solution to circulate *in vivo* for 5–10 min prior to sacrifice by exsanguination.

APPENDIX C

Radiochemical Procedures for Determination of ^{210}Po in Bioassay Samples

Bioassay Procedure for Polonium in Urine

1. Take 50 ml representative aliquot from 24-h urine sample.
2. Spike with ^{208}Po tracer.
3. Wet ash with concentrated HNO_3.
4. Dissolve ashed sample in 100 ml 1*N* HCl.
5. Transfer 10-ml aliquot to Ni plating cell.
6. Add 1 ml saturated ascorbic acid solution.
7. Adjust to 20 ml with 1*N* HCl.
8. Stir for 3 h at room temperature.
9. Remove Ni disc and rinse with ethanol.
10. Count disc on alpha spectrometer.

Bioassay Procedure for Polonium in Feces

1. Collect 24-h sample (10–300 g wet).
2. Dry in convection oven at 100°C for 2–3 days.
3. Homogenize dried feces in a screw-top container using a Spex Ball Mill Shaker.
4. Wet-ash 10% of sample with concentrated HNO_3 and $HClO_4$.
5. Adjust to 100 ml with 1*N* HNO_3.
6. Remove 10-ml aliquot, spike with ^{208}Po tracer and reduce to dryness.
7. Adjust to 20 ml with 1*N* HCl.
8. Transfer 10 ml to Ni plating cell.
9. Stir for 3 h at room temperature.
10. Remove Ni disc and rinse with ethanol.
11. Count on alpha spectrometer.

Bioassay Procedure for Polonium in Blood

1. Draw two 5–10-ml whole blood samples into vacutainer tubes containing heparin or ACD.

[9]Modified from Frank *et al.* (*6*).

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2. Hematocrit.
3. Centrifuge at 2000 rpm for 10 min.
4. Separate RBC, plasma and buffy coat.
5. Discard buffy coat.
6. Take 1 ml RBC and plasma and proceed with each separately.
7. Spike sample with ^{208}Po tracer.
8. Wet ash with concentrated HCl and HNO_3.
9. Dissolve ashed sample in 100 ml 1*N* HCl.
10. Transfer 10 ml to Ni plating cell.
11. Stir for 3 h at room temperature.
12. Remove Ni disc and rinse with ethanol.
13. Count on alpha spectrometer.

Bioassay Procedure for Polonium in Soft Tissue and Bone

1. Wet ash 50% of sample with concentrated HNO_3.
2. Adjust to 100 ml with 1*N* HNO_3.
3. Remove a 10-ml aliquot, spike with ^{208}Po tracer and reduce to dryness.
4. Dissolve ashed sample in 100 ml 1*N* HCl.
5. Transfer 2–50% (3–8 Bq) to Ni plating cell and adjust to 20 ml with 1*N* HCl.
6. Stir for 3 h at room temperature.
7. Remove Ni disc and rinse with ethanol.
8. Count on alpha spectrometer.

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