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CONSIDERATION OF AGE-DEPENDENT RADIUM RETENTION IN PEOPLE ON THE BASIS OF THE BEAGLE MODEL*

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ABSTRACT

The comparative toxicity of radium in beagles and humans is expected to provide a basis for interspecies extrapolation of other radionuclide dose-response relationships obtained with beagles. Information from beagle studies can also contribute to retrospective interpretation of human data. This paper examines in humans the proposition emanating from studies in beagles that long-term retention of radium varies in proportion to the calcium addition rate at the time of intake.

Because data on the calcium addition rate in younger humans were fragmentary, human calcium-addition rates were scaled from those in beagles, the relative calcium accretion rates in the two species at equivalent stages of skeletal growth providing the scaling factor. The variation of radium retention with age was determined by fitting a

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modified power function to data on the retention of radium from about 30 to 15000 days following a series of therapeutic injections of ^{226}Ra in humans ranging in age from 18 to 63 yr. The fractional retention R at t days following a single injection of ^{226}Ra was described by

$$R = (1 + t/d)^{-0.44} .$$

The age-dependent time constant d in the retention function was found to be proportional to the calcium addition rate at the time of injection in subjects receiving $< 200 \mu\text{g } ^{226}\text{Ra}$.

INTRODUCTION

A quantitative description of the relationship of alkaline-earth retention and age is relevant to the problem of risk estimation in human populations exposed to bone-seeking radionuclides. While the variation of the retention of calcium, strontium, and radium with age at intake has been described quantitatively in mice, rats, and dogs (Va58, Gl60, Sp64, Dec64, Del65, Pa78), alkaline-earth retention in man has largely been quantified only in adults (ICRP73). Retention by human subjects following a series of therapeutic injections of ^{226}Ra has been observed to be greater in those < 24 yr of age at injection than in those > 24 yr (ICRP73). Parks and his co-workers used these limited human data to make provisional estimates of the parameters of an age-dependent retention function derived from their analysis of radium retention in beagles (Pa78). The modified power function introduced by Tyler (Ty58) and used by Parks et al. (Pa78) to describe the fractional retention R at t days following a single injection of ^{226}Ra can be written

$$R = (1 + t/d)^b, \quad b < 0, \quad d > 0 \quad . \quad (1)$$

For beagles, the exponent b in Eq. 1 averaged -0.25 ± 0.03 for all but the highest dose-level dogs, and the age-dependent time constant d was expressed as

$$d = (2 + 135e^{-0.0114(\text{Age}-110)}) \text{day}, \quad \text{Age} > 110 \text{ day (Pa78)} \quad . \quad (2)$$

For humans, the exponent b in Eq. 1 was assigned the value -0.44 determined by Miller and Finkel (Mil65) and the age-dependent time constant d was expressed as

$$d = (0.04 + 2.72e^{-0.001(\text{Age}-4200)})_{\text{day}}, \text{ Age} > 4200 \text{ day (Pa78)}. \quad (3)$$

Parks and co-workers (Pa78) observed that the values of the time constant d in beagles obtained from Eq. 2 were proportional to the values of the calcium addition rate at the time of injection, obtained from the relationship between the calcium addition rate and age in beagles described by Marshall and Lloyd (Ma73).

This paper investigates the relationship between the long-term retention of radium in humans and the calcium addition rate, which is the total rate of long-term calcium transfer from blood to other body tissues, chiefly bone (ICRP73). It can also be defined as the sum of the calcium accretion rate and the calcium loss rate; the calcium accretion rate is the rate of change in body calcium, positive during growth, and the calcium loss rate is the total rate of long-term calcium transfer out of body tissues. In this paper, these rates are expressed as either a fraction or a percentage of the total body calcium per unit of time.

Estimates of the time constant d in Eq. 1 at various ages at intake of radium were obtainable from fits of Eq. 1 to the retention data of a group of human females therapeutically injected with ^{226}Ra , with the power-function exponent b being held at the average value for all subjects in the group. The expression $d = \phi A$ relating the

retention-function time constant d and the calcium addition rate A could then be fitted to the sets of values of d and age at intake. However, data on the relationship between the addition rate and age in humans were fragmentary, so that our first task was to generate estimates of the calcium addition rate in human females from data available in beagles.

ADDITION RATE HYPOTHESIS

A method was devised to estimate human addition rates from those in beagles. It was based on the hypothesis that, at equivalent stages of skeletal maturation, the rate of addition of calcium relative to its rate of loss is the same in humans and in dogs. Denoting the rates of calcium addition and loss by A and L , respectively, and using the subscripts h and c for the human and canine species, respectively, we can write the hypothesis as

$$A_h/L_h = A_c/L_c \quad , \quad (4)$$

where A_h and L_h are rates at age α_h , A_c and L_c are rates at age α_c , and the calcium content of the human at age α_h relative to the adult calcium content of the species is the same as that of the canine at age α_c .

Data were available on the calcium body content during growth in the two species, from which calcium accretion rates could be derived. The hypothesis can be restated explicitly in terms of the

calcium accretion rate M , which is the addition rate minus the loss rate. Substituting $A-M$ for L in Eq. 4, we can write

$$A_h = A_c M_h / M_c \quad . \quad (5)$$

Therefore, the age-equivalent accretion rates in the two species provide the factor by which the canine calcium addition rate can be scaled to humans.

CALCIUM ACCRETION

Calcium accretion in beagles has been described by Goldman (Go70). These accretion data were fitted by the logistic function CAD (Appendix I). On the other hand, estimates of the calcium content of younger humans were available only for boys, but most of the useful data on the retention of radium in humans was obtained from observations on females. Consequently, estimates of the calcium content of girls were derived from relationships between height and age, taken from Hamill et al. (Ha77) and shown in Fig. 1a, b, and the relationship between calcium content and age in boys, taken from Mitchell et al. (Mit45) and shown in Table 1.

The relationship between the 50th-percentile height and the calcium content of boys was derived from the height vs. age and calcium content vs. age data, and was described by the polynomial function CHB (Appendix I). On the assumption that the relationship between height and calcium content is the same in both sexes, the

50th-percentile heights of girls were transformed to calcium contents with the function CHB. The derived female calcium contents are listed in the third column of Table 1. Values for ages < 2 yr or > 18 yr were obtained by extrapolation. For subsequent usage, it was convenient to express the estimates of the calcium content of females < 18 yr of age by the function CAG-1 and those of females > 18 yr of age by the function CAG-2, which asymptotically approaches an adult value of 765 g (Appendix I).

The relationships between the calcium accretion rate and age in the two species are described by the fractional derivatives with respect to age of the beagle accretion function CAD and the human-female accretion functions CAG-1 and CAG-2 (Appendix I). These derivatives are plotted on the beagle age scale as Curves A (beagle accretion rate) and C (human accretion rate) in Fig. 2. The human ages equivalent to beagle ages during growth were calculated on the basis of percentage of adult calcium content. Our estimates indicated that 99% of the adult calcium content is acquired by age 270 days in the beagle and by about 19 yr in the human female. Age-scaling beyond these ages was done on the basis of percentage of mean lifespan. The mean lifespan was taken to be 16 yr for the beagle and 72 yr for the human female.

CALCIUM ADDITION

The relationship between the calcium addition rate and age in beagles was described by Marshall and Lloyd (Ma73) and is shown by

Curve B in Fig. 2. The calcium addition rate in human females was scaled from that in the beagle by the ratio of the age-equivalent calcium accretion rates in the two species, and is plotted on the beagle age scale as Curve D in Fig. 2. The calcium accretion and addition rates in human females are replotted on the human age scale as Curves E and F respectively in Fig. 3, the addition rate curve having been smoothed to a constant value between ages 10 and 16 yr.

The variation with age of the calcium addition rate A in human females is described by the expression

$$A = A_{\text{Min}} + A_{\text{Diff}} (1 - e^{-\kappa a}) \quad , \quad (6)$$

where $A_{\text{Min}} = 6.8\% \text{ yr}^{-1}$, the mean adult female value of A ,

$A_{\text{Diff}} = 21.8\% \text{ yr}^{-1}$, the difference between the virtually constant mean value of A in female adolescents aged 10 to 16 yr and A_{Min} ,

$a = 4.4 \cdot 10^5$,

$\kappa = 0.683 \text{ yr}^{-1}$,

and $\alpha = \text{age} > 10 \text{ yr}$.

The post-adolescent calcium addition rates predicted by Eq. 6 are similar to those calculated in ICRP20 (Fig. 1 in ICRP73) for low rates of bone apposition and resorption ($< 4.6\% \text{ yr}^{-1}$), and the higher addition rates for adolescents predicted by Eq. 6 are consistent with the higher bone formation rates observed by Frost in rib from humans aged 10-19 yr (Table 8 in ICRP73).

RADIUM RETENTION

Data on the retention of radium in ten human females who received weekly injections of 10 μg ^{226}Ra for medical reasons were compiled from the literature (Sc33, No55, Mil65, Mil69, ICRP73) and from data files at the Center for Human Radiobiology. Injection data and retention times for these persons are summarized in Table 2. Because the ^{226}F was administered over a period of time, a protracted-intake retention function was formulated by integrating Eq. 1 between the limits of time following last injection and time following first injection and dividing the time integral by the injection period. The protracted-intake retention function can be written

$$R = \frac{d^{-b}}{(1+b)\tau} \cdot [(t+d+\tau)^{1+b} - (t+d)^{1+b}] \quad , \quad (7)$$

where τ is the time from first to last injection of radium and t is the time following the last injection.

Fits of Eq. 7 to the retention data of each subject in Table 2 were carried out to obtain estimates of the parameters b and d . The geometric mean of the ten values of the exponent b was -0.44 with a geometric standard error of 1.16. This value of b is the same as the median determined for some of these same cases by Miller and Finkel (Mil65), and was used by Parks et al. in their provisional analysis of age-dependent retention in humans (Pa78).

Because d is very sensitive to variations in the power-function exponent b , the range of the best-fit values of d was extremely wide

and the relative standard deviations were large. The guidance drawn from beagle studies was that the exponent b could be considered age-invariant in the absence of severe radiation-induced metabolic perturbation (Dec64, Pa78). Therefore, Eq. 7 was fitted to the retention data of each subject in Table 2 with b constrained at the mean value of -0.44 . A much narrower distribution of d values having much-reduced relative standard deviations resulted from this second fit; these are listed in the last column of Table 2.

RADIUM RETENTION VS CALCIUM ADDITION

The sets of values of the power-function time constant d and the age at intake for the subjects in Table 2 were fitted with the function

$$d = \phi A \quad , \quad (8)$$

where ϕ (day^2) is a constant and A is the age-dependent calcium addition rate (Eq. 6), converted from units of $\% \text{ yr}^{-1}$ to units of day^{-1} by dividing by 36,525 $\% \text{ day yr}^{-1}$. The d values were weighted by the inverse square of the standard error. Eq. 8 acceptably fit the data of the six subjects who received $\leq 200 \mu\text{g } ^{226}\text{Ra}$, but not the data of the four subjects who received $> 200 \mu\text{g}$. The fit of Eq. 8 to the sets of d values and ages at intake of the subjects who received $\leq 200 \mu\text{g } ^{226}\text{Ra}$ produced a value of 248 ± 36 (S.E.) day^2 for the constant of proportionality ϕ . The time constant d in Eq. 1 or Eq. 6 is thus expressed as

$$d = \phi A = [0.046 + 0.148(1 - e^{-4.4 \cdot 10^5 e^{-0.683\alpha}})] \text{day} \quad , \quad (9)$$

where α = age $>$ 10 yr. The relative standard deviation of the distribution of d-values at a given age was estimated to be $\pm$ 36%.

The final adult value of d, 0.046 day, is close to the value of 0.04 day provisionally estimated by Parks et al., which is given by Eq. 3, but the shape of the curve generated by Eq. 9 is different from that generated by Eq. 3, which was obtained by simple analogy to the beagle results. Eq. 9 predicts a virtually constant value of d between ages 10 and 16 yr, after which there is a smooth transition to the adult value. The fit of Eq. 9 to the estimates of d for the subjects in Table 2 is shown in Fig. 4. As noted above, the data for the subjects who received $>$ 200 μg ^{226}Ra were excluded from the weighted least-squares fit.

One of the subjects in Table 2 who received $>$ 200 μg ^{226}Ra , Case 03-112, was suspected of having received additional injections after the initial measurements of residual body content of radium were made (Mil65,ICRP73), and another, Case 03-115, was previously reported to have been 25 yr of age at injection (Sc33,No55,Mil65,69,ICRP73), but more recently-acquired information alleges that she was about 20 yr of age. Also, the published injection period for Case 03-115 was considerably longer than that indicated in the hospital records of the subject (Mil65,69), so that she might have received less ^{226}Ra than the published amount listed in Table 2.

The age-dependent retention curves for two female subjects who were among those recently reported by Littman et al. (Li78) are

compared in Fig. 5 to the retention function proposed by Norris et al. (No55), $R = 0.54 t^{-0.52}$, $t \geq 1$ day. For the age-dependent retention curves in Fig. 5, the exponent b in Eq. 1 was assumed to have the value -0.44 and the values of d were obtained from Eq. 9. While there probably was an age-related difference in the retention of radium by the two subjects in Fig. 5, the estimates of absorbed dose to the skeleton for these and all other radium-exposed persons under study at the Center for Human Radiobiology are not affected by the age-dependence of the time constant d in the modified power function or the one-day intercept in the simple power function of Norris et al. (No55). The reason is that the dose estimates are based on measurements of radium body content made many years after the systemic intake. The virtual independence of the Center's dose estimates from the value of an age-dependent time constant or intercept is demonstrated in Appendix II.

SUMMARY AND CONCLUSIONS

The comparative metabolism of calcium and radium in humans and in beagles has been examined with the objective of quantifying the age-dependence of radium retention in humans. The variation of the calcium addition rate with age in humans was derived from that in beagles by the use of the age-equivalent calcium accretion rates in the two species. The estimates of post-adolescent calcium addition rates in humans were similar to those calculated in ICRP20 (ICRP73). The retention of radium in humans was shown to be proportional to the

estimates of the calcium addition rate at the time of injection, in agreement with a similar finding reported in beagles.

Estimates of absorbed dose to the skeleton for the population of dial painters exposed at young ages and being studied for health effects at the Center for Human Radiobiology are shown to be unaffected by the value of the proposed age-dependent time constant of the modified power function of radium retention. However, the greater retention of radium and greater bone-formation rates in younger humans suggest a considerably increased risk per unit intake of radium over that in adults.

APPENDIX I

MATHEMATICAL FUNCTIONS

A polynomial $F(x)$ of the form $a + bx + cx^2 + \dots$ is used if no other function is specified.

CHB: Calcium content (g) vs. height (cm) in boys

$CHB = F(x)$, where x is height.

Coefficients of $F(x)$: $a = 65.826$, $b = -1.307$, $c = 0.1116$,

$d = -1.187 \cdot 10^{-3}$, $e = 4.488 \cdot 10^{-6}$.

CAG-1,2: Calcium content (g) vs. age (yr) in girls

$CAG-1 = F(x)$, where x is age ≤ 18 yr.

Coefficients of $F(x)$: $a = 28.866$, $b = 62.043$, $c = -7.838$,

$$d = 0.7455, e = -0.02094.$$

$CAG-2 = ae^{-be^{-cx}}$, where x is age > 18 yr and e is the base of the natural logarithms.

$$\text{Coefficients: } a = 765, b = 2.66 \cdot 10^7, c = 1.15.$$

Calcium accretion rate (yr^{-1}) vs. age (yr) in girls

$$\frac{d(CAG-1)}{dx} \cdot \frac{1}{CAG-1} = F(x), \text{ where } x \text{ is age } < 18 \text{ yr.}$$

$$\text{Coefficients of } F(x): a = 62.043, b = -15.676, c = 2.2365, \\ d = -0.0838.$$

$$\frac{d(CAG-2)}{dx} \cdot \frac{1}{CAG-2} = bce^{-cx}, \text{ where } x \text{ is age } > 18 \text{ yr and } e \text{ is the base of the natural logarithms.}$$

Coefficients: as in CAG-2.

CAD: Calcium content (g) vs. age (days) in beagles

$$CAD = a(1 + be^{-cx})^{-1},$$

where x is age and e is the base of the natural logarithms.

$$\text{Coefficients: } a = 112.87, b = 29.733, c = 0.02924.$$

Calcium accretion rate (day^{-1}) vs. age (days) in beagles

$$\frac{d(CAD)}{dx} \cdot \frac{1}{CAD} = \frac{bce^{-cx}}{1 + be^{-cx}},$$

where x is age and e is the base of the natural logarithms.

Coefficients: as in CAD.

APPENDIX II

Estimates of absorbed dose to the skeleton for radium-exposed persons studied at the Center for Human Radiobiology are based on measurements of residual body content of radium at long times following systemic intake. As demonstrated below, these dose estimates are virtually independent of the age-dependent time constant d in the modified power function (Eq. 1) or the one-day intercept a in the simple power function of retention

$$R = a t^b, \quad a < 1 \text{ (day}^{-b}\text{)}, \quad b < 0, \quad t > 1 \text{ day} \quad . \quad (10)$$

The absorbed dose from the alpha particles of ^{226}Ra itself following a systemic intake is directly proportional to the product of the intake and the time integral of retention. Denoting by q_θ the ^{226}Ra body content measured at time θ following a single intake Q of ^{226}Ra , and denoting by T the time integral of the retention function at time τ following intake, we can write

$$QT = (q_\theta/R_\theta) \cdot \int_0^\tau R \, dt \quad , \quad (11)$$

where R is the fractional retention function for ^{226}Ra ,

and R_θ is the value of R at $t = \theta$.

For dose estimates based on the simple power function of Norris et al. (No55), the integral of R from $t = 0$ to $t = \tau$ in Eq. 11 is the sum of the integral from $t = 1$ day to $t = \tau$ of Eq. 10 and the integral from $t = 0$ to $t = 1$ day of a retention function R_{ζ_1} that has the value unity at $t = 0$ and the same value (a) and slope (ab) as Eq. 10 at $t = 1$ day. We can write

$$QT = \frac{q_0 \tau (\tau/\theta)^b}{(1+b)} \cdot (1 - F(a, b, \gamma, \tau)) , \quad b \neq -1 , \quad (12)$$

where $F(a, b, \gamma, \tau) = (1 - (1+b)\gamma/a)\tau^{-(1+b)} ,$

b and a respectively are the exponent and the one-day

intercept of the simple power function,

and γ is the time integral of retention at one day.

For dose estimates based on the modified power function, R in Eq. 11 is given by Eq. 1. We can write

$$QT = \frac{q_0 (\tau + d)}{(1+b)} \cdot \left(\frac{\tau + d}{\theta + d} \right)^b \cdot (1 - F(b, d, \tau)) , \quad b \neq -1 , \quad (13)$$

where $F(b, d, \tau) = (1 + \tau/d)^{-(1+b)}$

and b and d respectively are the exponent and the time constant of the modified power function.

When θ and τ are much greater than γ or d, $F(a, b, \gamma, \tau)$ in Eq. 12 and $F(b, d, \tau)$ in Eq. 13 are negligible, so that, whether R is a simple or a modified power function, we can write

$$QT \doteq \frac{q_0 \tau (\tau/\theta)^b}{(1+b)} . \quad (14)$$

Thus the Center's absorbed-dose estimates are virtually independent of the form of the power function and the exponent b is seen to be the only power-function constant upon which the dose estimates are significantly dependent. Similarly, estimates of absorbed dose from the alpha particles of ^{222}Rn and its decay products based on measurements of retained ^{222}Rn at long times after systemic intake of ^{226}Ra are virtually independent of the one-day intercept in the simple power function of Norris et al. that describes the variation of ^{222}Rn body content with time.

If the true power-function exponent were m , absorbed doses from ^{226}Ra , calculated from late measurements by use of the ^{226}Ra retention function of Norris et al. (No55, $b = -0.52$), would be $((1 + m)/0.48)$ times the true doses. Absorbed doses from ^{222}Rn and its decay products, calculated from late measurements by use of the ^{222}Rn retention function of Norris et al. (No55, $b = -0.28$), would be $((1 + n)/0.72)$ times the true doses if the true exponent were n .

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FIGURE CAPTIONS

Fig. 1a,1b. Height vs. age for girls (1a) and boys (1b). Data were taken from reference Ha77.

Fig. 2. Rates of calcium accretion and addition in beagles and humans at equivalent ages, plotted on the beagle age scale. Curve A was derived from the calcium accretion data in beagles reported by Goldman (Go70). Curve B is the calcium addition rate in beagles compiled by Marshall and Lloyd (Ma73). Curve C was derived from our estimates of calcium accretion in human females, with human ages scaled to beagle ages on the basis of percentage of adult calcium content during growth and percentage of mean lifespan thereafter. Curve D, the calcium addition rate in human females, is the product of Curve B and Curve C divided by Curve A.

Fig. 3. Rates of calcium accretion and addition in human females. Curves E and F respectively are Curves C and D in Fig. 2 replotted on the human age scale, the addition-rate curve having been smoothed to a constant value between ages 10 and 16 yr.

Fig. 4. The ^{226}Ra retention-function time constant d vs. age at injection in human females. The letter code beside each data point identifies each subject listed in Table 2. Values of d were obtained from fits of the modified power function $R = (1 + t/d)^{-0.44}$ to retained fractions of

injected ^{226}Ra observed in the subjects. The vertical brackets represent one standard error above and below the estimate of d . Circles and squares are data for subjects receiving $< 200 \mu\text{g}$ and $> 200 \mu\text{g}$ ^{226}Ra respectively. The curve is $d = \phi A$ fitted only to the data of subjects receiving $< 200 \mu\text{g}$, where A is the calcium addition rate function (Eq. 6, Curve F in Fig. 3, converted to units of day^{-1} from units of $\%$ yr^{-1}) and ϕ is a constant of proportionality, the best-fit value of which is 248 day^2 .

Fig. 5.

Comparison of the predicted fractional retention of ^{226}Ra in two subjects reported by Littman et al. (Li78), shown by the dashed curves, and the average fractional retention function of Norris et al. (No55), shown by the solid curve. The dashed curves are described by the function $R = (1 + t/d)^b$, where $b = -0.44$ and d is obtained from Eq. 9 (which is plotted in Fig. 4). The solid curve is described by the function $R = at^b$, where $a = 0.54$ and $b = -0.52$ (No55). The latter function was used by Littman et al. (Li78) to estimate doses in the two subjects. As shown in Appendix II, the areas under the curves of absolute retention vs. time for the two subjects, and hence the estimates of absorbed dose, are virtually independent of the time constant d or the one-day intercept a in the retention function, and are significantly dependent only on the value of the exponent b .

TABLE CAPTIONS

- Table 1. Calcium content vs. age in boys and girls. The data for boys were taken from Mitchell et al. (Mit45). The data for girls were estimated from those for boys on the basis of growth-curve comparisons (Fig. 1a,b).
- Table 2. ^{226}Ra dosages and retention times for ten human females (Sc33, No55, Mil65, Mil69, ICRP73) and best-fit values of the time constant d in the retention function $R = (1 + t/d)^b$ when the exponent b was constrained to the average value for all ten subjects, -0.44 . The letter in parentheses beside each case no. is the subject code used by Schlundt et al. (Sc33) and Norris et al. (No55). The observation period is the range of times from last injection to measurement of ^{226}Ra body content. The number of observations is the number of different times a measurement was made of both emanating and nonemanating ^{226}Ra body content and is the number of data points to which the retention function was fitted. Each value of fractional retention was weighted by its inverse in the least-squares estimation of the time-constant d .

Table 1. Calcium content vs. age in boys and girls. The data for boys were taken from Mitchell et al. (Mit45). The data for girls were estimated on the basis of growth-curve comparisons (Fig. 1a,b).

Age (yr)	Calcium Content (g)	
	Boys	Girls
0	28	25
1	100	104
2	147	133
3	179	159
4	201	186
5	219	214
6	239	245
7	264	280
8	297	320
9	341	363
10	396	409
11	463	457
12	539	508
13	624	557
14	715	605
15	806	649
16	894	688
17	973	720
18	1035	744
19	1073	759
20	1078	763

Table 2. ^{226}Ra dosages and retention times for ten human females (Sc33, No55, Mil65, Mil69, ICRP73) and best-fit values of the time-constant d in the fractional retention function $R = (1 + t/d)^b$ when the exponent b was constrained to the average value for all ten subjects, -0.44 . The letter in parentheses beside each case no. is the subject code used by Schlundt et al. (Sc33) and Norris et al. (No55). The observation period is the range of times from last injection to measurement of ^{226}Ra body content. The number of observations is the number of different times a measurement was made of both emanating and nonemanating ^{226}Ra body content and is the number of data points to which the retention function was fitted. Each value of fractional retention was weighted by its inverse in the least-squares estimation of the time-constant d .

Case No.	Age at First Injection (yr)	^{226}Ra Total Injected (μg)	Injection Period (days)	Observation Period (days)	No. of Observations	Time-Constant d ($\pm$ S.E.) (day)
03-101(A)	22.9	150	98	30-10326	5	0.0906 ± 0.0283
03-103(C)	53	150	98	201-7425	3	0.0229 ± 0.0128
03-109(I)	27.3	180	119	155-8005	4	0.0295 ± 0.0188
03-110(J)	31.8	200	133	130-12035	6	0.0512 ± 0.0084
03-111(K)	21.6	200	133	7210-15328	4	0.0490 ± 0.0095
03-112(L)	32.0	260	175	124-10444	4	0.181 ± 0.128
03-114(N)	30.1	360	245	30-11935	6	0.0066 ± 0.0043
03-115(O)	19.8	260	175	23-15209	7	0.0216 ± 0.0034
03-116(P)	24.0	250	168	30-15345	4	0.0379 ± 0.0131
03-125(T)	18.7	110	70	30-15376	6	0.207 ± 0.0204

FIGURE 1A

FIGURE 1B

FIGURE 3

FIGURE 4

FIGURE 5