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LONG-TERM RETENTION OF RADIUM IN FEMALE FORMER DIAL WORKERS*

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INTRODUCTION

Of all the bone-seeking metals, radium may well be unique in more than one respect. It is the only such element with alpha-particle emitting isotopes that has unequivocally produced serious biological effects, in particular bone sarcomas, in persons who acquired burdens of 3.66-day ^{224}Ra (Ma84) or the longer-lived ^{226}Ra (half-life 1600 years) with or without 5.75-year ^{228}Ra (Ro83). Furthermore, it is the only bone-seeking element whose metabolism in man has been studied in both the short and the very long terms. This paper is a contribution to our knowledge of the long-term metabolism. It presents strong presumptive evidence for an effect of radiation on the late retention of radium-226 in man.

SOURCE OF DATA

Studies in the U.S.A. of the late effects of radium in man were consolidated in 1969 in the newly created Center for Human Radiobiology (CHR), whose charter included metabolic and dosimetric studies. The current status of these studies is the subject of a recent paper (Ru84). An expandable computerized database, the CHR Information System (CHRIS), was established at an early stage. All new data were entered into the CHRIS, as were data that had been

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accumulated by previous contributors in the field of radium studies at Argonne National Laboratory/Argonne Cancer Research Hospital, at the Massachusetts Institute of Technology Radioactivity Center, and in the New Jersey Radium Research Project. One of the CHRIS files, VVRA, contains all the data on the measurements of radium *in vivo*, including those for 1916 former dial workers, the vast majority of whom were women.

THE DATA

The file VVRA was searched for the results of serial measurements of the radium contents of individuals, meeting certain criteria: (1) each individual must have been a female former dial worker; (2) there were to have been at least four observations of each individual's radium content starting in the 1950s with at least one in each completed decade since; and (3) the contents were to be at least 10 nCi to ensure a degree of reliability and to minimize statistical errors. Surprisingly, there were only 13 women who met all these criteria, and they had all worked at studios of the same Illinois dial company. Relevant data for these women are summarized in Table 1.

Table 1. Exposure and measurement data for 13 former dial workers.

Parameter	Median	Range
Age at first exposure	19	15-28
Year of first exposure	1922	1921-1925
Duration of exposure, y	2.0	0.4-4.0
Time from first exposure to first measurement, y	34.7	29-38
Age at first measurement	54	45-61
Year of first measurement	1958	1952-1959
Number of measurements	8	5-11
Most recent estimate of ^{226}Ra body content, nCi	230	12-1200

Six of the women continued working in the radium dial industry after 1925 but we do not include such employment in calculating the duration of exposure because recommendations were made in 1925 against the "pointing" of the radium-laden brush between the lips

(BLS29); radium intakes dropped rapidly for persons whose year of first exposure was subsequent to 1925 (Ru84).

With one exception, the periods of observation were >20 years; the exception was a 19.2-year period for one woman where the first of five measurements was made in January 1959 and the last in April 1978. Thus, the case still met the criteria for selection.

ANALYSIS OF DATA

It was assumed that the retention of radium 30-60 years after intake could be described by an exponential function of time, and such a function was fitted to the data for each woman by a computer method of least squares analysis, to yield values of the biological half-life, $t_{1/2}$ (years), and of the intercept, A_0 (nCi), at zero time. The data and fitted curves for the cases giving the shortest (15 y), the longest (90 y), and an intermediate value (31 y) for $t_{1/2}$ are plotted in Figure 1 to show the general quality of the data.

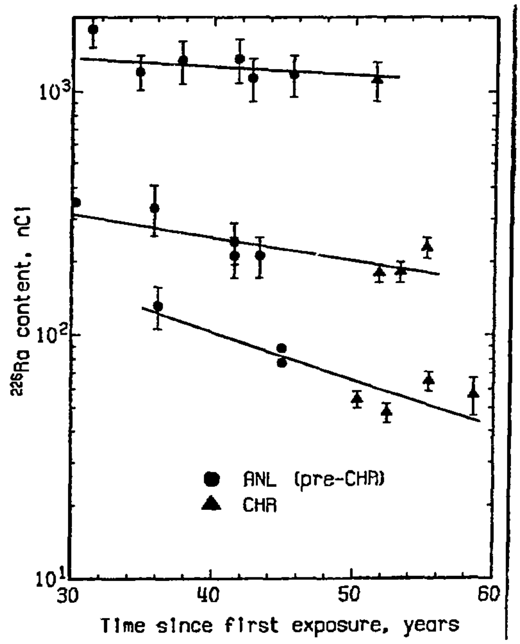

FIGURE 1 Data and fitted curves for subjects with biological half-lives of 90 y, 31 y and 15 y.

It is obvious from Figure 1 that the uncertainties on the half-lives are substantial. In this connection, some comments should be made on the standard errors represented by the vertical bars in Figure 1, and on the weighting used in the least squares analysis. The standard errors stored in the file VVRA and indicated in Figure 1 represent our best estimates of the absolute accuracy of the values for the radium contents, each being considered in isolation. For the intercomparison of estimates of the radium content of an individual, made by one investigator under comparable conditions, relative standard errors should be smaller, perhaps approaching the statistical error of counting. We have been unable to establish any kind of intercalibration between the results of the earlier investigators whose work is included with ours in the data. It is for this reason that the estimated errors of absolute accuracy are indicated in Figure 1, whereas weights in the least squares analyses were taken as the reciprocals of the values of the body contents.

RESULTS AND DISCUSSION

Values of λ, the elimination rate in percent of body content per year, were calculated from the relation,

$$\lambda = 69.3/t_{1/2} \quad .$$

In Figure 2, λ is plotted as a function of the body content at 45 years post-exposure, the latter being calculated from the expression,

$$A_{45} = A_0 e^{-0.45\lambda} \quad .$$

There is a strong

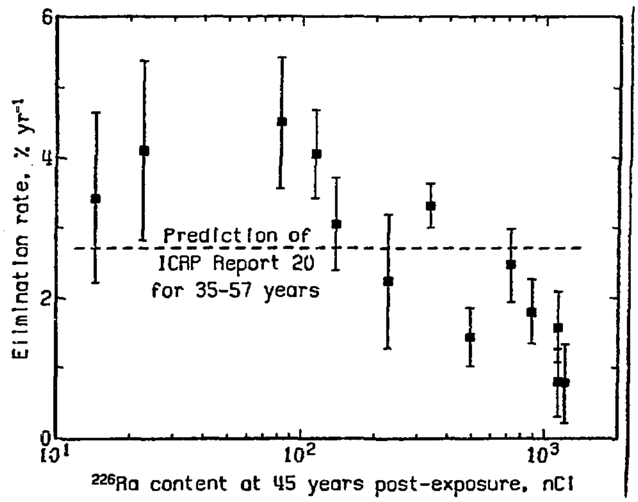

FIGURE 2 Elimination rate of radium at late times as a function of calculated radium content at 45 years (see text).

negative correlation between λ and A_{45} ($r = -0.88$, $p < 0.001$ for a two-tailed test), indicating an effect of radiation in the expected direction, i.e. an inhibition of bone resorption or remodelling at the higher radium contents. The horizontal dashed line in Figure 2 represents the average excretion rate (2.74 % yr^{-1}) for the interval 35-57 years predicted by the International Commission on Radiological Protection (ICRP) model of alkaline earth metabolism in man (IC73). It is in good agreement with the mean of the 13 values for λ (2.58 % yr^{-1}) but no allowances were made in the model for the effects of radiation, although the possibility was recognized.

A consequence of the correlation shown in Figure 2 is that the value of the intercept A_0 was proportionately greater than A_{45} for those subjects with the higher elimination rates, than for those with lower values of λ. Consequently, it can be argued that some of the persons with low values of A_{45} would have higher values of A_0 than some of those with high values of A_{45}, where we claim to have observed an effect of radiation. We would then have a paradox. Certainly the order of the subjects when they are sorted according to the values of A_{45} is different from the order when they are sorted according to A_0. However, there is still a reasonable correlation between λ and A_0 ($r = -0.64$, $p < 0.02$), supporting our hypothesis of an effect of radiation on the elimination rate.

There exists a measure of bone damage that has been shown to be strongly correlated with systemic intake of radium. This measure is the so-called "x-ray score" (Ke83), the sum of numbers assigned according to size, to lesions observed radiographically in 20 skeletal areas. Such scores exist for the 13 women of this study. When the score excludes values for bone sarcoma or pathological fracture, it is termed the "reduced x-ray score," and in Figure 3 this "reduced" score is plotted as the independent variable to show the strong correlation between it and the elimination rate, λ. A linear relationship was assumed and a least squares analysis yielded the plotted regression line; its upper and lower 95% confidence limits are drawn as dashed lines. The outlined point at a score of 21 was for a case where only 13 skeletal areas were examined. Had 20 areas been scored, a higher value might well have resulted, a possibility indicated by the arrow, but it is clear that the effect on the regression analysis would have been slight.

The results summarized in Figures 2 and 3 represent strong but not conclusive evidence for an effect of the radiation on the late retention of radium in these subjects. We can add one further piece

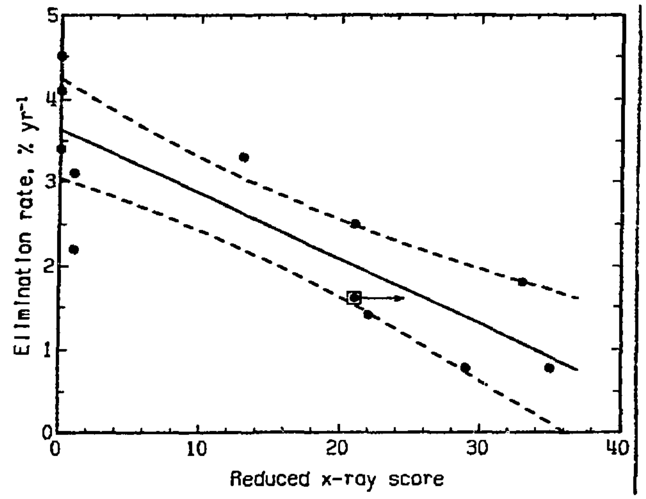

FIGURE 3 Elimination rate as a function of reduced x-ray score for the 13 subjects.

of evidence derived from data on radium concentrations in soft tissues from eight different subjects who died 40-53 years post-exposure (Sc82). If the fractional rate of elimination of radium does vary as the inverse of the total amount present, then the levels in blood and soft tissues should be proportionately lower at the higher body contents. Figure 4 shows that this is the case for soft tissues.

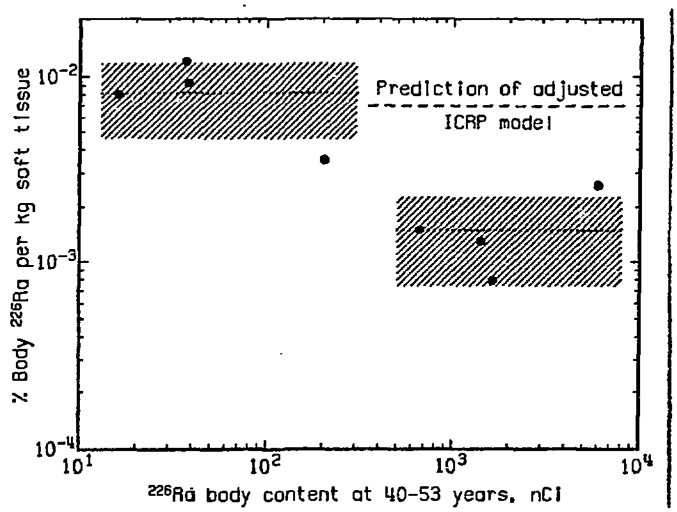

FIGURE 4 Relative concentration of ^{226}Ra in soft tissues as a function of terminal body content, for 8 subjects (Sc82).

It is tempting to draw a straight line through the data but there is no rationale for doing so when both axes have logarithmic scales.

Also the results are for widely disparate numbers of samples; seven of the subjects had between one and four samples analyzed, while for one subject the number was 29. The data were divided into two groups by body content (below and above 400 nCi ^{226}Ra) and mean values were calculated. In Figure 4 these values are indicated as dotted lines at 8.2×10^{-3} % kg^{-1} and 1.5×10^{-3} % kg^{-1} for the two groups respectively. The shaded areas represent the spread of two standard errors on either side of the mean values. The prediction of the ICRP model was 3.6×10^{-2} % kg^{-1}, above the range of the ordinate scale in Figure 4, but an adjusted model (Sc82) that improved the fit to experimental data yielded an expected value of 7.0×10^{-3} % kg^{-1} as indicated by the dashed line.

There remain two other possibilities to explain the trend shown in Figure 2, namely, the age at which radium was acquired and the length of the exposure period. The analysis made in the development of the ICRP model of alkaline earth metabolism demonstrated an age-effect on retention depending on whether the subject was younger or older than 24 at the time of radium intake (IC73). In our series, six of the 13 women were aged 18 or less at the time they started work with radium paint so skeletal growth may have been incomplete.

Variability in the duration of exposure may also affect long-term retention by virtue of different dose rates: intake of a given amount in a short period may result in higher local concentrations ("hot spots") and higher dose rates compared to intake of the same amount over a protracted period.

As a test of the possible contributions to the causes of the variability in λ, a multivariate analysis was performed. The prediction equation was: $\lambda = a + bA_{45} + cY_{fxp} + dD_w$, where a, b, c, and d were constants to be determined, A_{45} was as already defined, Y_{fxp} was the age in years at first exposure, and D_w was the duration of exposure in weeks. The results, summarized in Table 2, confirm that the body content at late times is by far the most important factor controlling the variability in λ, the contributions of the others not being significant. We conclude that we have detected an effect of radiation on the long-term retention of radium.

Table 2. Results of multivariate analysis for the prediction of λ.

Parameter	Constant	Estimate	± S.E.	Significance level
Intercept	a	4.99	0.95	0.0005
^{226}Ra content at 45 yrs	b	-0.0027	0.0004	0.0001
Age at first exposure	c	-0.07	0.05	0.14
Duration of exposure	d	0.003	0.003	0.26
	$r^2 = 0.83$, $p < 0.0008$			

Qualitatively similar findings have been reported for radium in dogs (L176, Pa78). However, the doses were higher and the periods of observation were much smaller fractions of the lifespan, so it is not possible to make a detailed comparison.

SUMMARY

The results of measurements of the radium contents of 13 women made over periods of about 20 or more years have been extracted from our files. The women were all employed at different studios of the same Illinois plant as luminous dial workers for periods of up to 4 years, starting at ages 15 to 28 in the early 1920s. The data for each woman were fitted by an exponential function of time, yielding a value for the biological half-life at roughly 30-60 years after first exposure to radium. There was a strong negative correlation between the elimination rate and the body content, suggesting an effect of radiation on bone resorption or remodelling.

We also observed a strong negative correlation between the elimination rate and the "reduced x-ray score," a measure of bone damage observed radiographically in the same subjects. Age at first exposure and duration of exposure were not significantly correlated with the elimination rate. The concentration of radium in soft tissues from eight other subjects, expressed as a percentage of the terminal radium content, decreased with increasing body content, providing further evidence that radiation was affecting the elimination rate. We conclude that an effect of radiation on the late retention of radium has been demonstrated.

ACKNOWLEDGMENTS

Determinations of radium in vivo at ANL in the early 1950s were made by W. P. Norris. Subsequent measurements at ANL prior to the formation of CHR were made by Miller (Mi69).

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