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RETENTION AND ELIMINATION OF RADIUM ISOTOPES PRODUCED
BY THE DECAY OF THORIUM PARENTS WITHIN THE BODY -
CALCULATIONS AND COMPARISON WITH
EXPERIMENTAL FINDINGS

by

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November 1957

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Operated by The University of Chicago
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Contract W-31-109-eng-38

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RETENTION AND ELIMINATION OF RADIUM ISOTOPES PRODUCED BY THE DECAY OF THORIUM PARENTS WITHIN THE BODY - CALCULATIONS AND COMPARISON WITH EXPERIMENTAL FINDINGS

ABSTRACT

Radium daughters are produced in vivo by radioactive decay of thorium isotopes in the body and partially eliminated by metabolic processes. If the assumption is made that the radium formed gains access to the general circulation and it is retained according to the law $R(t) = (1 - b)t^{-b}$, it is possible to calculate the elimination of Ra from the body as a function of time, and the radioactive equilibrium of Ra to Th in vivo. These calculations have been performed for the case of a single administration of thorium (masses 227, 228, 229, 230 and 232) and for values of b extending from 0.1 to 0.9.

Comparison with results reported in the literature shows good agreement in cases of noncolloidal deposits of thorium.

In the case of thorotrast ($\text{Th}^{232}\text{O}_2$) patients the agreement is poor, but it can be improved by making the assumption that only a fraction of the radium formed in soft tissue is available to the general circulation. These calculations, in conjunction with some reported observations, imply that the radioactivity present in the skeleton of an average thorotrast patient is equivalent to 0.5 - 1.0 M.P.L. (maximum permissible level) on a dosimetric basis; hence, follow-up of these patients should add materially to the subject of the chronic toxicity of boneseekers in humans.

To facilitate eventual analysis in terms of metabolic compartments, the radium retention functions have also been expressed as the sums of four exponential terms for periods of time ≤ 200 days; the ratios of the activity of the radium daughters to that of the thorium parents, as calculated by this procedure, agree with the calculations based on the power function.

A. INTRODUCTION

L. D. Marinelli

The evaluation of the long-term radiotoxicity of the several isotopes of thorium is complicated by the fact that widely different patterns of deposition occur when this element, in its many chemical forms, gains access to the mammalian body through various routes.

At present, direct clinical experience is limited to groups of patients who were injected with thorotrast as far back as thirty years ago,⁽¹⁾ and, to a lesser extent, to personnel of long-established industrial concerns.⁽²⁾ It seems increasingly clear, however, that greater use of this type of information can be made if the pathology observed in either group can be stated in terms of absorbed dose in situ and of such pertinent parameters as relative biological effect (RBE) and dose rate, etc. The findings will be of great aid in describing the long-term effects of low level radiation in liver, spleen and possibly the bone marrow and lung. The existence of sustained efforts along these lines is evident from the various reports recently published.

Essential to the statement of the absorbed dose is the description of the state of equilibrium of the radioactive chain in vivo due to differential elimination of daughter products.

Early quantitative inquiries on this subject,⁽³⁾ conducted with thorotrast-injected patients were not successful, owing to the inadequacy of the instrumentation existing at the time and to the several complicating circumstances arising from the growth and chemical behavior of the various elements of the chain of Th^{232} in a colloidal suspension both in vitro and in vivo. The situation, however, seems to have cleared considerably in later years.⁽⁴⁻⁷⁾

Recent reports on equilibrium studies of soluble Th^{228} deposited in the skeleton of dogs^(8,9) and of Th^{227} accidentally introduced into a human⁽¹⁰⁾ have offered the possibility of evaluating the usefulness of theoretical studies pertinent to less complex circumstances.

The essence of these studies is the concern of parts B, C and D of this report. The basic assumptions underlying the calculations are as follows:

1. Thorium is administered only once in complete absence of its daughters.
2. No thorium is eliminated by the mammalian body.
3. The radium daughter produced by the thorium parent behaves as though injected into the blood stream.

The second assumption is well justified by the negligible excretion of thorium reported over varying periods of time.^(5,8,9,10) It is felt, therefore, that whatever excretion of the Th parent takes place in any particular instance can be accounted for most simply by a single multiplicative factor.

The third assumption leads to the adoption of an equation of radium retention $R(t)$ at time t (in days) of the form

$$R(t) = A t^{-b}$$

where A and b are constants, and, to a first approximation, $A = 1 - b$. The validity of the general form of this equation has been amply verified for radium intravenously injected in several species.^(11,12)

The calculations reported herein express the retention of radium in the body as the ratio of the radioactivity of radium to that of the thorium parent, and the expected elimination rate of the radium daughter as the fraction of the activity of the thorium existing in vivo.^{*} These factors can be compared directly with experimental results obtainable either by measurement of gamma activity in vivo or by examination of radioactivity in excreta and organ specimens. Conversely they may be of aid in establishing the whole body contents in accidental cases if measurements of the more abundantly eliminated radium daughter are available.

The calculations have been extended to several values of the constant b in order to facilitate comparison with prospective experimental data dealing with different thorium compounds in various animal species, and to long periods of time in order to anticipate the absorbed dose ensuing throughout the lifetime of the host. For the convenience of the investigator interested in short range experiments (≤ 200 days) and in absorbed doses in various metabolic compartments, some of these calculations have been repeated in the appendix of this report with the retention pattern expressed as a sum of four exponential terms, each sum corresponding to a specific value of b.

Comparison with experiments is treated in Section E. In Part I and II the subjects of noncolloidal and thorotrast injections are discussed. In Part III, the results from Section C, combined with experimental values reported in the literature, are applied to the evaluation of the over-all activity of the skeleton of an average thorotrast patient.

^{*}Other parameters descriptive of the lack of radioactive equilibrium in vivo, such as ratio of rates of production and elimination of radium, can be easily derived from these expressions.

B. ANALYTICAL EXPRESSIONS

J. C. Reynolds and P. F. Gustafson

If radium is injected intravenously into a mammal, the retention of the element is given by the empirical formula

$$R_c(t) = (1 - b)t^{-b} \text{ for } t \geq 1$$

where $R_c(t)$ is the fraction of the original dose which remains in the body and t is the time in days since the dose was given. The constant b varies from about 0.2 to 0.7 depending upon the animal species.⁽¹¹⁾

Using this expression for $R_c(t)$, it is possible to derive an expression for the retention of radium which is continually produced by the radioactive decay of the thorium parent deposited within the body. This retention will be affected by four processes:

1. Chemical elimination of the thorium
2. Radioactive decay of the thorium
3. Chemical elimination of the radium
4. Radioactive decay of the radium.

The first process is sufficiently slow to be negligible within the span of a human lifetime. To determine the combined effect of the remaining three processes, let the initial amount of thorium (at $t = 0$) be equal to unity. At any later time τ , the amount of radium being produced is $\lambda_T e^{-\lambda_T \tau}$, where λ_T is the decay rate of the thorium. At a still later time t , chemical elimination will have reduced this amount of radium by a factor of $R_c(t - \tau)$, and radioactive decay will have reduced the retained fraction by a factor $e^{-\lambda_R(t - \tau)}$, where λ_R is the decay rate of the radium. Thus the amount of radium remaining at time t due to radium production within times τ and $\tau + d\tau$ is:

$$\lambda_T e^{-\lambda_T \tau} R_c(t - \tau) e^{-\lambda_R(t - \tau)} d\tau,$$

and the total amount $R(t)$ of radium retained at time t is

$$R(t) = \int_0^t \lambda_T e^{-\lambda_T \tau} R_c(t - \tau) e^{-\lambda_R(t - \tau)} d\tau,$$

or substituting $u = t - \tau$ and $du = -d\tau$,

$$R(t) = \lambda_T e^{-\lambda_T t} \int_0^t e^{-(\lambda_R - \lambda_T)u} R_c(u) du.$$

From this expression for $R(t)$, we may derive the "in vivo" ratio $A(t)$ of the activity of the radium to the activity of the thorium:

$$A(t) = \frac{\lambda_R R(t)}{\lambda_T e^{-\lambda_T t}} = \lambda_R \int_0^t e^{-(\lambda_R - \lambda_T)u} R_c(u) du \quad .$$

A third function, the rate of chemical elimination (i.e., excretion) may also be derived. The rate of change of $R(t)$ is the sum of three factors: the rate of production of radium from thorium, the rate of radioactive decay of the radium, and the rate of chemical elimination. If the daily rate of chemical elimination of radium is designated as $B(t)$, we have

$$\frac{d}{dt} R(t) = \lambda_T e^{-\lambda_T t} - \lambda_R R(t) + B(t) \quad .$$

Substituting the expression derived for $R(t)$ and solving for $B(t)$ gives

$$B(t) = \lambda_T e^{-\lambda_T t} \left[e^{-(\lambda_R - \lambda_T)t} R_c(t) - 1 + \frac{\lambda_R - \lambda_T}{\lambda_R} A(t) \right]$$

Finally, in analogy to $A(t)$, we may define an "elimination ratio" $E(t)$, as the ratio between the activity of the radium excreted daily at time t to the activity of the thorium present in the body at the same time. Thus

$$E(t) = \frac{\lambda_R B(t)}{\lambda_T e^{-\lambda_T t}} = \lambda_R \left[e^{-(\lambda_R - \lambda_T)t} + R_c(t) - 1 + \frac{\lambda_R - \lambda_T}{\lambda_R} A(t) \right] \quad .$$

The calculation of $A(t)$, and $E(t)$ has been carried out for five pairs of thorium and radium isotopes. The results are shown in Sections C and D.

C. THE RATIO $A(t)$ OF THE ACTIVITIES OF Ra AND Th IN VIVO

J. C. Reynolds

It would be possible to calculate $A(t)$ by means of direct integration of

$$A(t) = \lambda_R \int_0^t R_c(u) e^{-(\lambda_R - \lambda_T)u} du$$

if an analytical expression for $R_c(t)$ were available for all positive values of t . We already have

$$R_c(0) = 1$$

$$R_c(t) = (1 - b) t^{-b} \quad \text{for } t \geq 1.$$

To complete this definition, we must define $R_c(t)$ in some arbitrary but reasonable manner for $0 < t < 1$. Let us set $R_c(t)$ in this interval equal to a second-degree polynomial $p(t) = c_1 + c_2 t + c_3 t^2$ whose three coefficients are determined by the three conditions

$$p(t) = 1 \quad \text{at } t = 0$$

$$p(t) = (1 - b) t^{-b} \quad \text{at } t = 1$$

$$\frac{d}{dt} p(t) = \frac{d}{dt} [(1 - b) t^{-b}] \quad \text{at } t = 1$$

Solving this set of conditions for c_1 , c_2 , and c_3 completes the definition of the chemical retention function:

$$R_c(t) = \begin{cases} 1 - (b + b^2) t + b^2 t^2 & \text{for } 0 \leq t \leq 1 \\ (1 - b) t^{-b} & \text{for } 1 \leq t < \infty \end{cases}$$

If we substitute this definition into the integral for $A(t)$, we obtain

$$A(t) = \lambda_R \left[\int_0^1 [1 - (b + b^2)u + b^2 u^2] e^{-(\lambda_R - \lambda_T)u} du + (1 - b) \int_1^t u^{-b} e^{-(\lambda_R - \lambda_T)u} du \right] \\ \text{for } t \geq 1,$$

or

$$A(t) = \lambda_R \left[\int_0^1 [1 - (b+b^2)u + b^2u^2 - (1-b)u^{-b}] e^{-\lambda u} du + (1-b) \lambda^{b-1} \Gamma_{\lambda t}(1-b) \right] \quad \text{for } t \geq 1,$$

where $\lambda = \lambda_R - \lambda_T$.

The integral remaining in this equation may be approximated by expanding the exponential term into a power series. The result is an alternating power series in λ . The first two terms give an approximation,

$$\int_0^1 [1 - (b+b^2)u + b^2u^2 - (1-b)u^{-b}] [1 - \lambda u + \dots] du \simeq \alpha(b) - \lambda \beta(b)$$

where

$$\alpha(b) = -\frac{1}{2}b - \frac{1}{6}b^2$$

$$\beta(b) = \frac{1}{2} - \frac{1}{3}b - \frac{1}{12}b^2 - \frac{(1-b)}{(2-b)},$$

with an error which is smaller than 0.01λ .⁽²⁾ Since $\lambda < 0.19$ in all cases under consideration, the resulting error will be less than 0.0004, or less than 0.12%.

The incomplete gamma function $\Gamma_u(1+p)$ may be expressed in terms of the function

$$I\left(\frac{u}{\sqrt{1+p}}, p\right) = \frac{\Gamma_u(1+p)}{\Gamma_\infty(1+p)} = (1+p) \frac{\Gamma_u(1+p)}{\Gamma_\infty(2+p)}$$

which is tabulated in Pearson's Tables of the Incomplete Gamma Function.

As a final expression for the activity ratio, we have

$$A(t) = \lambda_R \left[\alpha(b) - \lambda \beta(b) + \lambda^{b-1} \Gamma_\infty(2-b) I\left(\frac{\lambda t}{\sqrt{1-b}}, -b\right) \right]$$

A medium-speed electronic computer was used to compute $A(t)$ and $E(t)$, from prepared tables of $\alpha(b)$, $\beta(b)$, $\Gamma_\infty(2-b)$, and $I\left(\frac{\lambda t}{\sqrt{1-b}}, -b\right)$. Since the values given in Pearson's tables were too widely spaced to allow accurate linear interpolation, it was necessary to limit the computation to pre-selected values of $\frac{\lambda t}{\sqrt{1-b}}$ for which I was given in the tables. Thus, the

computer began with values of $\frac{\lambda t}{\sqrt{1-b}}$, I , b , λ_R , and λ_T , and calculated the corresponding values of t , $A(t)$, and $E(t)$. Values of I for $\frac{\lambda t}{\sqrt{1-b}} = 0.1, 0.2, 0.5, 1, 1.5, 2, 3.5$, and 5 were taken from Pearson's tables. In addition, I was calculated for $\frac{\lambda t}{\sqrt{1-b}} = 0.003, 0.01$, and 0.03 by means of the approximation

$$\Gamma_x(1-b) = x^{-b} \left[\frac{x}{1-b} - \frac{x^2}{1!(2-b)} + \frac{x^3}{2!(3-b)} - \dots \right]$$

In this and all succeeding computations the following daily decay rates were used:

Ra ²²³	0.061888	Th ²²⁷	0.037266
Ra ²²⁴	0.19043	Th ²²⁸	0.00099950*
Ra ²²⁵	0.046834	Th ²²⁹	2.5872×10^{-7}
Ra ²²⁶	1.1708×10^{-6}	Th ²³⁰	2.3738×10^{-8}
Ra ²²⁸	0.00028344	Th ²³²	1.3662×10^{-13}

In certain of these five cases, the machine computations did not cover the full range of $1 \leq t \leq 30,000$ days in which we are interested. Additional values for t smaller than the machine computations were calculated from the approximation

$$A(t) \simeq \lambda_R [\alpha(b) + t^{1-b}]$$

which is valid for small λ and λt . Values in the tables which were computed by this method are indicated by an asterisk.

It was not necessary to make separate calculations for large t , since in this region $A(t)$ is asymptotic to

$$A(\infty) = \lambda_R [\alpha(b) - \beta(b) \lambda + \lambda^{b-1} \Gamma_{\infty}(2-b)]$$

This value was included in the machine computation and is given in the tables under $t = 30,000$ when it is within 0.1% of the actual value of $A(30,000)$.

A comparison of the values of the activity ratio as calculated directly and as calculated by means of the exponential approximation of $R_c(t)$ * shows excellent agreement except for values of t of the order of a few days. The discrepancy here is due to the difference in the two definitions of $R_c(t)$ for $0 \leq t \leq 1$, and is a direct consequence of the arbitrariness of defining any retention or elimination function for such small values of t . The discontinuity inherent in actual retention and elimination prevents either $R_c(t)$ or $A(t)$ from having any real meaning for values of t of the order of one day.

*See Section F (Appendix).

TABLE C-I
ACTIVITY RATIO $\text{Th}^{227} - \text{Ra}^{223}$

<u>b = 0.1</u>		<u>b = 0.2</u>		<u>b = 0.3</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
1.16	0.0664	1.09	0.0589	1.02	0.0519
3.85	0.196	3.63	0.160	3.40	0.131
7.71	0.353	7.27	0.273	6.80	0.211
19.3	0.712	18.2	0.514	17.0	0.371
38.5	1.09	36.3	0.756	34.0	0.523
57.8	1.32	54.5	0.895	51.0	0.608
77.1	1.45	72.7	0.977	68.0	0.659
135	1.62	127	1.08	119	0.721
193	1.65	182	1.10	170	0.736
30,000	1.67	30,000	1.11	30,000	0.742
<u>b = 0.4</u>		<u>b = 0.5</u>		<u>b = 0.6</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
3.15	0.106	2.87	0.0844	2.57	0.0664
6.29	0.162	5.74	0.124	5.14	0.0927
15.7	0.267	14.4	0.192	12.8	0.135
31.5	0.362	28.7	0.250	25.7	0.170
47.2	0.414	43.1	0.281	38.5	0.188
62.9	0.445	57.4	0.299	51.4	0.199
110	0.483	101	0.322	89.9	0.213
157	0.493	144	0.329	128	0.217
30,000	0.496	30,000	0.332	30,000	0.219
<u>b = 0.7</u>		<u>b = 0.8</u>		<u>b = 0.9</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
2.22	0.0510	1.82	0.0378	1.28	0.0270
4.45	0.0678	3.63	0.0476	2.57	0.0314
11.1	0.0933	9.08	0.0615	6.42	0.0372
22.2	0.113	18.2	0.0718	12.8	0.0415
33.4	0.123	27.2	0.0772	19.3	0.0437
44.5	0.130	36.3	0.0805	25.7	0.0451
77.9	0.138	63.6	0.0851	45.0	0.0473
111	0.141	90.8	0.0867	64.2	0.0481
30,000	0.142	30,000	0.0878	30,000	0.0490

TABLE C-II
ACTIVITY RATIO Th^{228} - Ra^{224}

<u>b = 0.1</u>		<u>b = 0.2</u>		<u>b = 0.3</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
1.00	0.165	2.36	0.293	2.21	0.251
2.50	0.341	4.72	0.439	4.42	0.363
5.01	0.528	7.08	0.522	6.63	0.426
7.51	0.639	9.44	0.572	8.83	0.463
10.0	0.705	16.5	0.632	15.5	0.508
17.5	0.785	23.6	0.647	22.1	0.520
25.0	0.803	30,000	0.651	30,000	0.524
30,000	0.809				
<u>b = 0.4</u>		<u>b = 0.5</u>		<u>b = 0.6</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
2.04	0.212	1.87	0.178	1.67	0.146
4.09	0.298	3.73	0.242	3.34	0.194
6.13	0.345	5.60	0.277	5.01	0.219
8.18	0.373	7.47	0.297	6.68	0.233
14.3	0.407	13.1	0.323	11.7	0.253
20.4	0.416	18.7	0.330	16.7	0.258
30,000	0.419	30,000	0.333	30,000	0.261
<u>b = 0.7</u>		<u>b = 0.8</u>		<u>b = 0.9</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
1.45	0.118	1.18	0.0930	1.67	0.0822
2.89	0.151	2.36	0.114	2.50	0.0878
4.34	0.169	3.54	0.125	3.34	0.0914
5.78	0.179	4.72	0.132	5.84	0.0967
10.1	0.193	8.26	0.141	8.35	0.0989
14.5	0.197	11.8	0.145	30,000	0.101
30,000	0.200	30,000	0.147		

TABLE C-III
ACTIVITY RATIO $\text{Th}^{229} - \text{Ra}^{225}$

<u>b = 0.1</u>		<u>b = 0.2</u>		<u>b = 0.3</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
2.03	0.0821	1.91	0.0706	1.79	0.0603
4.05	0.149	3.82	0.122	3.57	0.0990
10.1	0.301	9.55	0.231	8.93	0.176
20.3	0.463	19.1	0.340	17.9	0.250
30.4	0.559	28.6	0.403	26.8	0.291
40.5	0.616	38.2	0.440	35.7	0.315
70.9	0.685	66.8	0.486	62.5	0.345
101	0.701	95.5	0.496	89.3	0.352
30,000	0.706	30,000	0.500	30,000	0.355
<u>b = 0.4</u>		<u>b = 0.5</u>		<u>b = 0.6</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
1.65	0.0510	1.51	0.0426	1.35	0.0351
3.31	0.0801	3.02	0.0641	2.70	0.0504
8.27	0.134	7.55	0.101	6.75	0.0754
16.5	0.183	15.1	0.133	13.5	0.0957
24.8	0.210	22.6	0.150	20.3	0.106
33.1	0.225	30.2	0.160	27.0	0.113
57.9	0.245	52.8	0.173	47.3	0.121
82.7	0.250	75.5	0.177	67.5	0.123
30,000	0.252	30,000	0.178	30,000	0.125
<u>b = 0.7</u>		<u>b = 0.8</u>		<u>b = 0.9</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
1.17	0.0283	1.91	0.0288	1.35	0.0205
2.34	0.0387	4.77	0.0380	3.38	0.0247
5.85	0.0547	9.55	0.0449	6.75	0.0277
11.7	0.0671	14.3	0.0485	10.1	0.0293
17.5	0.0735	19.1	0.0507	13.5	0.0303
23.4	0.0774	33.4	0.0537	23.6	0.0318
40.9	0.0825	47.7	0.0548	33.8	0.0324
58.5	0.0842	30,000	0.0556	30,000	0.0330
30,000	0.0851				

TABLE C-IV
ACTIVITY RATIO $\text{Th}^{230} - \text{Ra}^{226}$

<u>b = 0.1</u>		<u>b = 0.2</u>		<u>b = 0.3</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
100	$7.37 \times 10^{-5}*$	100	$4.66 \times 10^{-5}*$	100	$2.91 \times 10^{-5}*$
300	19.9 etc.*	300	11.2 etc.*	300	6.30 etc.*
1000	58.5*	1000	29.3*	1000	14.6*
2480	133	2340	58.0	2190	25.5
8270	391	7800	151	7290	59.0
24,800	1040	23,400	362	21,900	126
<u>b = 0.4</u>		<u>b = 0.5</u>		<u>b = 0.6</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
10	$0.439 \times 10^{-5}*$	10	$0.336 \times 10^{-5}*$	10	$0.252 \times 10^{-5}*$
30	0.875 etc.*	30	0.608 etc.*	30	0.415 etc.*
100	1.83*	100	1.14*	100	0.696*
300	3.56*	300	2.00*	300	1.03*
1000	7.35*	1000	3.66*	1000	1.81*
2030	11.2	1850	5.00	1650	2.23
6750	23.1	6160	9.14	5510	3.62
20,300	44.5	18,500	15.8	16,500	5.63
<u>b = 0.7</u>		<u>b = 0.8</u>		<u>b = 0.9</u>	
<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>	<u>t (days)</u>	<u>A (t)</u>
10	$0.183 \times 10^{-5}*$	10	$0.127 \times 10^{-5}*$	10	$0.0790 \times 10^{-5}*$
30	0.273 etc.*	30	0.172 etc.*	30	0.0972 etc.*
100	0.415*	100	0.236*	100	0.117*
300	0.562*	300	0.295*	300	0.135*
1000	0.876*	1000	0.407*	827	0.161
1430	0.985	1170	0.422	1000	0.165*
4780	1.42	3900	0.548	2760	0.189
14,300	2.01	11,700	0.701	8270	0.220
				27,600	0.256

*See page 10 for method of calculation of these values.

TABLE C-V
ACTIVITY RATIO $\text{Th}^{232} - \text{Ra}^{228}$

b = 0.1		b = 0.2		b = 0.3	
t (days)	A (t)	t (days)	A (t)	t (days)	A (t)
10.0	0.00224	9.47	0.00168	8.86	0.00126
33.5	0.00663	31.6	0.00444	29.5	0.00297
100	0.0177	94.7	0.0106	88.6	0.00643
335	0.0507	316	0.0272	295	0.0146
669	0.0906	631	0.0455	590	0.0230
1670	0.182	1580	0.0848	1480	0.0397
3350	0.279	3160	0.124	2950	0.0556
5020	0.337	4730	0.147	4430	0.0644
6690	0.371	6310	0.160	5900	0.0697
11,700	0.412	11,000	0.177	10,300	0.0762
16,700	0.422	15,800	0.181	14,800	0.0778
30,000	0.425	30,000	0.182	30,000	0.0783
b = 0.4		b = 0.5		b = 0.6	
t (days)	A (t)	t (days)	A (t)	t (days)	A (t)
8.20	0.000937	7.48	0.000692	6.69	0.000504
27.3	0.00199	24.9	0.00133	22.3	0.000878
82.0	0.00389	74.8	0.00235	66.9	0.00141
273	0.00791	249	0.00429	223	0.00232
547	0.0117	499	0.00596	446	0.00304
1370	0.0187	1250	0.00886	1120	0.00420
2730	0.0250	2490	0.0113	2230	0.00515
4100	0.0285	3740	0.0127	3350	0.00565
5470	0.0305	4990	0.0135	4460	0.00595
9560	0.0331	8730	0.0144	7810	0.00633
13,700	0.0337	12,500	0.0147	11,200	0.00644
30,000	0.0340	30,000	0.0148	30,000	0.00650
b = 0.7		b = 0.8		b = 0.9	
t (days)	A (t)	t (days)	A (t)	t (days)	A (t)
5.80	0.000358	4.73	0.000243	3.35	0.000154
19.3	0.000558	15.8	0.000345	11.2	0.000194
58.0	0.000832	47.3	0.000468	33.5	0.000236
193	0.00124	158	0.000631	112	0.000287
386	0.00153	316	0.000739	223	0.000318
966	0.00198	789	0.000895	558	0.000360
1930	0.00232	1580	0.00101	1120	0.000391
2900	0.00250	2370	0.00107	1670	0.000407
3860	0.00261	3160	0.00111	2230	0.000417
6760	0.00275	5520	0.00116	3900	0.000432
9660	0.00280	7890	0.00118	5580	0.000438
30,000	0.00283	30,000	0.00119	30,000	0.000445

FIG. C-1: ACTIVITY RATIO Th 227 - Ra 223

FIG. C-2: ACTIVITY RATIO Th 228 - Ra 224

FIG. C-4b: ACTIVITY RATIO $\text{Th}^{230} - \text{Ra}^{226}$ FIG. C-4c: ACTIVITY RATIO $\text{Th}^{230} - \text{Ra}^{226}$

D. THE ELIMINATION RATE OF Ra EXPRESSED AS A RATIO
OF THE ACTIVITY OF THE Th IN VIVO

J. C. Reynolds

The power function for $R_c(t)$

$$R_c(t) = (1 - b)t^{-b} \text{ for } t \geq 1$$

may be substituted in the expression ratio

$$E(t) = \lambda_R \left[e^{-\lambda t} R_c(t) - 1 + \frac{\lambda}{\lambda_R} A(t) \right]$$

giving

$$E(t) = \lambda_R \left[e^{-\lambda t} (1 - b)t^{-b} - 1 + \frac{\lambda}{\lambda_R} A(t) \right] \text{ for } t \geq 1$$

where $\lambda = \lambda_R - \lambda_T$.

The evaluation of $E(t)$ by this formula was included in the machine computation described previously.

When necessary, values of $E(t)$ for values of t smaller than the range covered by the machine computation were calculated from the approximation

$$E(t) \simeq \lambda_R [(1 - b)t^{-b} - 1]$$

Values calculated in this manner are indicated by an asterisk.

For values of t larger than those covered by the machine computation, the asymptotic value of $E(t)$ was used:

$$E(t) \simeq \lambda_R \left[\frac{\lambda}{\lambda_R} A(\infty) - 1 \right]$$

Values calculated by this method are indicated by a double asterisk.

TABLE D-I
RADIUM ELIMINATION $\text{Th}^{227}\text{-Ra}^{223}$

b = 0.1		b = 0.2		b = 0.3	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.16	0.00690	1.09	0.0131	1.02	0.0186
3.85	0.0128	3.63	0.0230	3.40	0.0311
7.71	0.0157	7.27	0.0272	6.80	0.0362
19.3	0.0186	18.2	0.0315	17.0	0.0408
38.5	0.0199	36.3	0.0334	34.0	0.0425
57.8	0.0205	54.5	0.0341	51.0	0.0431
77.1	0.0207**	72.7	0.0344	68.0	0.0433
135	0.0207**	127	0.0344	119	0.0436**
193	0.0207**	182	0.0346**	170	0.0436**
30,000	0.0207**	30,000	0.0346**	30,000	0.0436**
b = 0.4		b = 0.5		b = 0.6	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
3.15	0.0375	2.87	0.0429	2.57	0.0472
6.29	0.0426	5.74	0.0478	5.14	0.0515
15.7	0.0468	14.4	0.0514	12.8	0.0546
31.5	0.0487	28.7	0.0528	25.7	0.0558
47.2	0.0493	43.1	0.0534	38.5	0.0561
62.9	0.0493	57.4	0.0535	51.4	0.0564
110	0.0495	101	0.0537**	89.9	0.0565**
157	0.0497**	144	0.0537**	128	0.0565**
30,000	0.0497**	30,000	0.0537**	130	0.0565**
				30,000	0.0565**
b = 0.7		b = 0.8		b = 0.9	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
2.22	0.0505	1.82	0.0537	1.28	0.0564
4.45	0.0543	3.63	0.0567	2.57	0.0587
11.1	0.0570	9.08	0.0587	6.42	0.0599
22.2	0.0577	18.2	0.0595	12.8	0.0602
33.4	0.0582	27.2	0.0595	19.3	0.0607
44.5	0.0583	36.3	0.0596	25.7	0.0607**
77.9	0.0584	63.6	0.0597	45.0	0.0607**
111	0.0584**	90.8	0.0597**	64.2	0.0607**
112	0.0584**	93.0	0.0597**	74.4	0.0607**
130	0.0584**	112	0.0597**	93.0	0.0607**
30,000	0.0584**	130	0.0597**	112	0.0607**
		30,000	0.0597**	130	0.0607**
				30,000	0.0607**

**Values calculated as described on page 20.

TABLE D-II
RADIUM ELIMINATION $\text{Th}^{228}\text{-Ra}^{224}$

b = 0.1		b = 0.2		b = 0.3	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.00	0.0174	2.36	0.0529	2.21	0.0737
2.50	0.0285	4.72	0.0616	4.42	0.0848
5.01	0.0339	7.08	0.0647	6.63	0.0882
7.51	0.0357	9.44	0.0658	8.83	0.0898
10.0	0.0364	16.5	0.0668	15.5	0.0909
17.5	0.0370	23.6	0.0669	22.1	0.0912
25.0	0.0371	347	0.0671**	347	0.0912**
347	0.0372	694	0.0671**	694	0.0912**
694	0.0372**	1390	0.0671**	1390	0.0912**
1390	0.0372**	2770	0.0671**	2770	0.0912**
2770	0.0372**				
b = 0.4		b = 0.5		b = 0.6	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
2.04	0.0920	1.87	0.108	1.67	0.122
4.09	0.104	3.73	0.120	3.34	0.134
6.13	0.108	5.60	0.124	5.01	0.138
8.18	0.109	7.47	0.126	6.68	0.139
14.3	0.111	13.1	0.127	11.7	0.141
20.4	0.111	18.7	0.127	16.7	0.141
347	0.111**	347	0.127**	347	0.141**
694	0.111**	694	0.127**	694	0.141**
1390	0.111**	1390	0.127**	1390	0.141**
2770	0.111**	2770	0.127**	2770	0.141**
b = 0.7		b = 0.8		b = 0.9	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.45	0.135	1.18	0.146	1.67	0.166
2.89	0.146	2.36	0.157	2.50	0.169
4.34	0.149	3.54	0.160	3.34	0.170
5.78	0.151	4.72	0.161	5.84	0.171
10.1	0.152	8.26	0.162	8.35	0.171
14.5	0.153	11.8	0.163	347	0.171**
347	0.153**	347	0.163**	694	0.171**
694	0.153**	694	0.163**	1390	0.171**
1390	0.153**	1390	0.163**	2770	0.171**
2770	0.153**	2770	0.163**		

**Values calculated as described on page 20.

TABLE D-III
RADIUM ELIMINATION $\text{Th}^{229}\text{-Ra}^{225}$

b = 0.1		b = 0.2		b = 0.3	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
2.03	0.00726	1.91	0.0134	1.79	0.0187
4.05	0.00956	3.82	0.0172	3.57	0.0234
10.1	0.0119	9.55	0.0208	8.93	0.0273
20.3	0.0131	19.1	0.0225	17.9	0.0292
30.4	0.0135	28.6	0.0230	26.8	0.0297
40.5	0.0136	38.2	0.0232	35.7	0.0301
70.9	0.0138	66.8	0.0234	62.5	0.0302**
101	0.0138	95.5	0.0234	89.3	0.0302**
5000	0.0138**	5000	0.0234**	5000	0.0302**
30,000	0.0138**	30,000	0.0234**	30,000	0.0302**
b = 0.4		b = 0.5		b = 0.6	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.65	0.0232	1.51	0.0272	1.35	0.0306
3.31	0.0282	3.02	0.0322	2.70	0.0353
8.27	0.0324	7.55	0.0360	6.75	0.0389
16.5	0.0340	15.1	0.0377	13.5	0.0402
24.8	0.0346	22.6	0.0380	20.3	0.0407
33.1	0.0348	30.2	0.0382	27.0	0.0409
57.9	0.0349	52.8	0.0384	47.3	0.0409
82.7	0.0349	75.5	0.0385**	67.5	0.0409
5000	0.0351**	5000	0.0385**	5000	0.0410**
30,000	0.0351**	30,000	0.0385**	30,000	0.0410**
b = 0.7		b = 0.8		b = 0.9	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.17	0.0337	1.91	0.0404	1.35	0.0425
2.34	0.0380	4.77	0.0429	3.38	0.0444
5.85	0.0411	9.55	0.0438	6.75	0.0449
11.7	0.422	14.3	0.0440	10.1	0.0451
17.5	0.0425	19.1	0.0442	13.5	0.0453
23.4	0.0427	33.4	0.0442	23.6	0.0453
40.9	0.0429	47.7	0.0442	33.8	0.0453
58.5	0.0429	5000	0.0442**	5000	0.0453**
5000	0.0429**	30,000	0.0442**	30,000	0.0453**
30,000	0.0429**				

**Values calculated as described on page 20.

TABLE D -IV
RADIUM ELIMINATION Th^{230} - Ra^{226}

b = 0.1		b = 0.2		b = 0.3	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.00	$0.117 \times 10^{-6*}$	1.00	$0.234 \times 10^{-6*}$	1.00	$0.351 \times 10^{-6*}$
10	0.333*	10	0.582	10	0.760*
30	0.421*	30	0.695*	30	0.873*
100	0.508*	100	0.799*	100	0.967*
300	0.577*	300	0.873*	300	1.02*
1000	0.641*	1000	0.937*	1000	1.07*
2480	0.691	2340	0.972	2190	1.09
8270	0.745	7800	1.02	7290	1.12
24,800	0.784	23,400	1.05	21,900	1.13
b = 0.4		b = 0.5		b = 0.6	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.00	$0.469 \times 10^{-6*}$	1.00	$0.587 \times 10^{-6*}$	1.00	$0.700 \times 10^{-6*}$
10	0.893*	10	0.986*	10	1.06*
30	0.991*	30	1.07*	30	1.11*
100	1.06*	100	1.12*	100	1.14*
300	1.10*	300	1.13*	300	1.15*
1000	1.13*	1000	1.15*	1000	1.16*
2030	1.14	1850	1.16	1650	1.16
6750	1.15	6160	1.16	5510	1.17
20,300	1.16	18,500	1.16	16,500	1.17
b = 0.7		b = 0.8		b = 0.9	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.00	$0.819 \times 10^{-6*}$	1.00	$0.937 \times 10^{-6*}$	1.00	1.06×10^{-6}
10	1.10*	10	1.13*	10	1.15*
30	1.14*	30	1.15*	30	1.16*
100	1.16*	100	1.16*	100	1.17*
300	1.16*	300	1.17*	300	1.17*
1000	1.17*	1000	1.17*	827	1.17
1430	1.17*	1170	1.17	1000	1.17*
4780	1.17*	3900	1.17	2760	1.17
14,300	1.17*	11,700	1.17	8270	1.17
				27,600	1.17

*Values calculated as described on page 20.

TABLE D-V
RADIUM ELIMINATION Th^{232} - Ra^{228}

b = 0.1		b = 0.2		b = 0.3	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.00	$0.284 \times 10^{-4*}$	1.00	$0.566 \times 10^{-4*}$	1.00	$0.851 \times 10^{-4*}$
10.0	0.809×10^{-4}	9.47	1.39	8.86	1.80
33.5	1.04×10^{-4}	31.6	1.70	29.5	2.12
100	1.22	94.7	1.92	88.6	2.30
335	1.39	316	2.10	295	2.47
670	1.48	631	2.18	590	2.53
1670	1.56	1580	2.26	1480	2.57
3350	1.60	3160	2.30	2950	2.59
5020	1.62	4730	2.30	4430	2.61
6690	1.63	6310	2.32	5900	2.61
11,700	1.63	11,000	2.32	10,300	2.61
16,700	1.63	15,800	2.32	14,800	2.61
b = 0.4		b = 0.5		b = 0.6	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.00	$1.13 \times 10^{-4*}$	1.00	$1.42 \times 10^{-4*}$	1.00	$1.70 \times 10^{-4*}$
8.20	2.10	7.48	2.32	6.69	2.47
27.3	2.39	24.9	2.55	22.3	2.66
82.0	2.53	74.8	2.68	66.9	2.74
273	2.64	249	2.74	223	2.78
547	2.68	499	2.76	446	2.80
1370	2.72	1250	2.78	1120	2.80
2730	2.74	2490	2.78	2230	2.82
4100	2.74	3740	2.80	3350	2.82
5470	2.74	4990	2.80	4460	2.82
9560	2.74	8730	2.80	7810	2.82
13,700	2.74	12,500	2.80	11,200	2.82
b = 0.7		b = 0.8		b = 0.9	
t (days)	E(t)	t (days)	E(t)	t (days)	E(t)
1.00	$1.98 \times 10^{-4*}$	1.00	$2.26 \times 10^{-4*}$	1.00	$2.55 \times 10^{-4*}$
5.80	2.59	4.73	2.68	3.35	2.74
19.3	2.72	15.8	2.78	11.2	2.80
58.0	2.78	47.3	2.80	33.5	2.82
193	2.80	158	2.82	112	2.82
386	2.82	316	2.82	223	2.82
966	2.82	789	2.82	558	2.84
1930	2.82	1580	2.82	1120	2.84
2900	2.82	2370	2.82	1670	2.84
3860	2.82	3160	2.82	2230	2.84
6760	2.82	5520	2.82	3900	2.84
9660	2.82	7890	2.82	5580	2.84

*Values calculated as described on page 20.

FIG.D-1: RADIUM ELIMINATION $\text{Th}^{227} - \text{Ra}^{223}$ FIG.D-2: RADIUM ELIMINATION $\text{Th}^{228} - \text{Ra}^{224}$

FIG. D-3: RADIUM ELIMINATION $\text{Th}^{229} - \text{Ra}^{225}$ FIG. D-4: RADIUM ELIMINATION $\text{Th}^{230} - \text{Ra}^{226}$

FIG.D-5: RADIUM ELIMINATION $\text{Th } 232 - \text{Ra } 228$

E. COMPARISON WITH EXPERIMENT

L. D. Marinelli

I. Noncolloidal Thorium Compounds

Earliest evidence of the success of theoretical calculations similar in form to some of those developed in sections B, C, and D, of this report was obtained in the study of body retention and rate of elimination of Ra^{226} inhaled accidentally in the form of sulphate.⁽¹³⁾

In that case, both the amount of the "fictitious" parent (represented by the amount of radium in the lung) and its "decay" constant (in reality, the rate of removal of Ra from the lung) were obtained experimentally in vivo. It was found that when the value of the retention constant $b = 0.5$, found by Norris, et al.⁽¹²⁾ in intravenously injected patients, was applied to the calculations, the latter yielded results in agreement with both the retention of the whole body and the excretion rates as observed by independent experiments covering relatively long periods of time.

Later, in June 1954, the occurrence of an accidental puncture contaminated with the chloride of Th^{227} , offered the opportunity to investigate the growth of the Ra^{223} daughter in vivo and its rate of elimination. The experimental results, as well as the comparison with theory, have been published in full^(10,14) and need not be repeated here. It should be recalled, however, that the numerical value of the constant b which yielded good agreement with experimental observations was 0.7 instead of the average value of 0.5 found by Norris et al.⁽¹²⁾ in chronic radium patients. It is impossible to state at this juncture whether this discrepancy is due to statistical variations to be expected in humans, or whether it is a consequence of subtle chemical processes (involving radium) occurring during repair of the flesh wound where Th^{227} was initially deposited. It is of interest in this regard that the ratios of the activities of the Ra^{223} to that of Th^{227} , both at the site of injury and in the body as a whole, were not too dissimilar, and that the removal of Th^{227} from the puncture was rather rapid.

A factor not considered at the time,* which would have led to an apparently greater value of b , could have been the unsuspected elimination of Pb^{211} (36 minutes) since another lead isotope, Pb^{212} (10.6 hrs), has been reported to exist in vivo in amounts ranging from about 0.45 to 0.17 of the

*The gamma-ray spectroscopic analysis was run for Th^{227} and Ra^{223} + daughters in equilibrium without specific inquiry as to whether the short lived daughters of Ra^{223} were actually in equilibrium.

equilibrium Ra^{224} value in liver and spleen of patients injected with thoro-trast many years before.⁽⁷⁾ The relevance of these findings to our observations in vivo and in the excreta is doubtful, however, because the much shorter life of Pb^{211} would have led, under ordinary circumstances, to its almost complete disintegration in the bladder and in the intestinal tract, even if removed instantly from the site of thorium deposition. If this had not been the case, a sharp disagreement would have arisen between whole body readings and activity of the excreta since any Pb^{211} activity therein would have been missed, owing to the relatively long time intervening between sample collection and measurement.

Absence of this inconsistency in our observations leads us to believe that a prompt removal of Pb^{211} in situ* would have not affected the value of b for the body as a whole. The possibility of its existence, however, deserves full consideration in the future, since it does affect the local absorbed dose. As matters stand now, the observed activity ratios at the site of injury and of the body as a whole (Tables IV and II of Ref. 10) do not exclude the possibility that at the former site Pb^{211} was not in equilibrium with Ra^{223} .

Another source of material which permits direct comparison between experimental observations and the calculations reported herein is found in the controlled experiments reported by Van Dilla et al.^(8,9) on beagles injected with soluble Th^{228} . These authors have reported on gamma-ray activity measurements in vivo and on radioactivity growth of carcasses and portions of a humerus soon after death. Their reported value of $\text{Ra}^{224}:\text{Th}^{228}$ activity ratio for the whole carcass is around 0.6 beyond 10 days** after injection of a solution of Th^{228} carrier free, in a citric acid-sodium citrate buffer solution of pH 3.5 and a total citrate concentration of 0.24 meq/l. Our calculations for $b = 2$ obtained from their observations⁽¹⁵⁾ on the retention of Ra^{226} in the same breed of dogs yield an activity ratio $A(t) = 0.64$, in excellent agreement with their findings.***

The agreement between our calculations and the experimental results mentioned above suggests that in these particular instances the entire amount of radium produced by the thorium parent becomes available to the general circulation as though it were injected intravenously. In view of the well-known preference which radium exhibits for bone, the retention of radium by the whole body is, essentially, a measure of the retention of the

*By "in situ" is meant the location where Pb^{211} is "born."

**Comparison at earlier dates is complicated by the fact that the injected Th^{228} was in equilibrium with its daughters, but the comparison is valid after periods of time of the order of 15 days.

***The excretion of Ra^{224} in these Th^{228} dogs has been found to decrease with increasing time ($t > 100$ days) and dose levels.⁽¹⁷⁾ The authors are inclined to attribute this decrease to both skeletal and kidney radiation damage.

whole skeleton. However, because of the simplified assumptions made, our calculations throw no light on the local variations of deposition in bone; all that can be surmised at the moment is that because of the prolonged "injection" of radium, these "hot spot" variations are likely to be less pronounced than they would be in the case of a single injection of radium under comparable physiological conditions. The degree to which this phenomenon occurs is likely to depend, among other things, on the decay constants of both elements.

Prima-facie evidence that only a fraction f of the radium produced in vivo is available to the general circulation could be claimed whenever activity ratios in vivo are higher, and conversely, when elimination rates are lower than those indicated by the type of calculation shown in this report. To justify this claim further it is essential, however, to corroborate the time behavior of these ratios since values at any one time could often be matched by adjusting either or both f and b in the general equation of radium retention. Unfortunately, the experimental data on $\text{Ra}^{224}:\text{Th}^{228}$ and on $\text{Ra}^{223}:\text{Th}^{227}$ equilibrium in dogs (18) and rats (19) where these animals were injected with Ra^{228} and Ac^{227} , respectively, are not sufficiently explicit to justify at this time a thorough comparison with our theoretical approach.

II. Thorotrast Injections

In the case of thorotrast injection, presence of the numerous daughter products of the Th^{232} chain, and of several complicating factors of chemical nature preclude valid comparison between the experimental and calculated transport of the radium daughters in vivo. The importance of these factors has been discussed in the literature^(5,6,7) and their evaluation has led to realistic appraisals of the absorbed dose in the reticulo-endothelial system of patients injected with thorotrast. The interested reader is referred to the original sources for details.

Our analysis of the thorotrast dosimetry will be limited instead to the skeleton in order to assess to what extent observations on this group of patients can contribute to the "radium toxicity" problem. To this purpose, the numerical data available⁽⁵⁻¹⁰⁾ on relative $\text{Ra}:\text{Th}$ equilibrium in vivo, have been summarized in Table E-I. Shown in this table is the retentive factor, f , namely, the observed ratio of the amount of radium daughter present in the organ where thorium is deposited to the amount of the radium daughter that would have been present therein at the time of observation if no metabolic removal had taken place. It is apparent from the table that, in cases of long-standing thorotrast deposits, about $2/3$ of the radium grown in vivo is held at the original site of deposition of thorium, namely liver and spleen,* and that, therefore, only about $1/3$ is available to

*The observations of Gustafson, et al.⁽¹⁰⁾ suggest a similar high retentive value ($f=0.82$) in muscle at 6 days but a much lower value (~ 0.14) after 1 month in the case of ThCl_4 contamination.

the general circulation. This, in turn, suggests that the fundamental equation of retention of the radium which reaches circulation should be modified to

$$R(t) = (1-f)(1-b)t^{-b} \quad 0 < f < 1$$

for purposes of comparison with observed whole-body retention and excretion rates. The only pertinent data available at the present time are the Ra^{224} excretion rates measured by Hursh.⁽⁵⁾ It will be seen that the value of b consistent with observation of both excretion rates (12%) and the value of $f = 0.7$ in spleen and liver is $b = 0.25$, which is distinctly smaller than Norris' value of $b = 0.5$. This disagreement, however, cannot be considered real because the data are pooled from a very small group of patients in whom thorotrast had been deposited for widely different periods of time. Agreement within the limits of error of measurement and sampling, is instead, suggested by the fact that a value of $f = 0.82$ in Hursh's patient (well within the range of 0.5-1.0 observed by Rotblat et al.⁽⁶⁾) would have yielded a value of $b = 0.5$.

It is obvious that at this point more precise values of the constant b should be obtained by observations on excretion rates of the patients scheduled for splenectomy and that efforts should be applied to the evaluation of f in live thorotrast patients with known excretion rates by means of gamma-ray spectrometry in vivo.*

These supplemental tasks are likely to be rewarding inasmuch as they may lead to a realistic appraisal of the radioactivity of the skeleton in this relatively large group of patients. At present, no thoroughly reliable estimate is possible since certain details necessary to accurate dosimetry are lacking; yet the following exploratory calculations of skeletal burden should prove of value to interested investigators.

III. Estimated Skeletal Activity of Thorotrast Patients.

It will be assumed that the average thorotrast patient has retained⁽²¹⁾ $4 \mu\text{g}$ of Th^{232} corresponding to an activity of $0.44 \mu\text{c}$. The estimates of the amounts of daughter products lodged in bone are as follows:

Ra^{228}

Although the amount of Ra^{228} present in a thorotrast suspension will vary on account of its shelf age and time of preparation after thorium

*This technique has been illustrated in various publications from this laboratory.⁽²⁰⁾ The alternative technique of quantitative autoradiography⁽⁶⁾ of skeletal tissue, besides suffering from the obvious limitation of sample size, seems impractical (at least as far as the measurement of Ra^{224} and Bi^{212} is concerned) because of the very small quantities involved. It is well worth applying, however, to the evaluation of Ra^{228} and Th^{232} because of the directness of approach to the dosimetry in situ.

separation from the ore, the amount reaching the skeleton is likely to be minimal on account of either plating in vitro⁽⁶⁾ or inaccessibility to the circulation in vivo.⁽⁵⁾ A significant amount of Ra^{228} grown in vivo must reach the circulation, however, because, on the average, the retentive factor in liver and spleen has been found^(6,7) to be of the order of: $f_{\text{Ra}^{228}} = 0.7$ after 10-15 years. On the basis of $b = 0.5$ in the retention equation mentioned above, and on the assumption that radium is wholly retained by the skeleton, the calculated Ra^{228} skeletal load will be: $\text{Ra}^{228} = (1 - f_{\text{Ra}^{228}}) \times 0.015 = 0.3 \times 0.015 = 0.005$ of the Th^{232} activity after long periods of time. This value is to be reduced to roughly 0.004 in order to take into account the slow growth of Ra^{228} in vivo. According to the only data available,⁽¹⁸⁾ this source should be in equilibrium with its daughter products.

Th^{228}

The Th^{228} in the colloidal suspension is assumed to be retained in liver and spleen similarly to Th^{232} and, hence, not available to osseous tissue.⁽⁵⁾ As for the Th^{228} grown in vivo, however, Rundo⁽⁷⁾ reports a retention factor $f_{\text{Th}^{228}} = 0.8$ at $t = 10-15$ years for liver and spleen.* Nothing is known about the location of the missing fraction in humans. If, upon its release from liver and spleen, Th^{228} is assumed to act as a colloidal Th^{232} suspension, little or none would be found in the skeleton,⁽²¹⁾ being relocated, perhaps, in the marrow. If it should behave, instead, as a buffered injected solution most of it (~ 0.85) should find its way to bone.^{(8)**} At equilibrium, then, the activity of skeletal Th^{228} would be expected to be between zero and a maximum:

$$\text{Th}^{228} = (1 - f_{\text{Th}^{228}}) \times f_{\text{Ra}^{228}} \times 0.85 = 0.2 \times 0.7 \times 0.85 = 0.12 \text{ of } \text{Th}^{232} \text{ activity.}$$

This Th^{228} deposit, however, should not be expected to be in equilibrium with its daughter products⁽⁸⁾; for $b = 0.5$ the activity of Ra^{228} would be expected to be $1/3$ of this (vide supra).

Ra^{224}

The original amount of Ra^{224} in the thorotrast solution is irrelevant to the dosimetric problem at hand because of its short life. As for the amount grown in vivo and reaching the skeleton, the most direct estimate

*Hursh et al., in a case of 19-year standing⁽⁵⁾ report for what is essentially $f_{\text{Ra}^{228}} \times f_{\text{Th}^{228}}$, a value between 0.4 and 0.65 in ten different tissues. This is in good over-all agreement with the values assumed here.

**Evidence consistent with migration of Th^{228} to bone following thorotrast injections comes from Stenstrom's observations on rabbits (Ref. 4, Table IV). They indicate an increase of bone α -ray activity of the order of 10% within a six-day period, presumably due to the growth of Ra^{224} in the presence of a more active deposit of Ra^{228} .

can be made from the data of Hursh⁽⁵⁾ indicating an excretion rate at equilibrium equal to 0.12 times the rate at which Ra^{224} is being produced, or 0.023 of the activity of Th^{228} . On the assumption of $b = 0.5$, (Tables C-II, D-II) the amount retained in bone would be equivalent in activity to $0.33/0.127 = 2.6$ times the daily rate of excretion, namely equal to 0.06 of the Th^{228} present in the reticulo-endothelial system; hence: $\text{Ra}^{224} = 0.06 \times f_{\text{Ra}^{228}} \times f_{\text{Th}^{228}} = 0.06 \times 0.7 \times 0.8 \approx 0.033$ of the Th^{232} activity. All daughters of Ra^{224} in bone should be expected to be at about 0.9 equilibrium because of the limited release of Em^{220} . (8,22)

On the basis of the foregoing, the probable limits of the total radioactivity in bones of thorotrast patients would be, in terms of Th^{232} activity (round figures):

$$\text{Minimum} = 0.004 \text{ Ra}^{228} + 0.004 \text{ Th}^{228} + 0.04 \text{ Ra}^{224} + 0.04 \text{ Em}^{220} \text{ (equil.)}$$

$$\text{Maximum} = 0.004 \text{ Ra}^{228} + 0.12 \text{ Th}^{228} + 0.08 \text{ Ra}^{224} + 0.07 \text{ Em}^{220} \text{ (equil.)}$$

For an average Th^{232} deposit of 4g ($0.44 \mu\text{c}$), these activities (in curies) correspond to:

$$\text{Minimum: } 1.8 \times 10^{-9} \text{ Ra}^{228} + 1.8 \times 10^{-9} \text{ Th}^{228} + 1.9 \times 10^{-8} \text{ Ra}^{224} + 1.7 \times 10^{-8} \text{ Em (equil.)}$$

$$\text{Maximum: } 1.8 \times 10^{-9} \text{ Ra}^{228} + 5.5 \times 10^{-8} \text{ Th}^{228} + 3.7 \times 10^{-8} \text{ Ra}^{224} + 3.3 \times 10^{-8} \text{ Em (equil.)}$$

In terms of Ra^{226} α -ray energy equivalence (11 Mev per Ra^{226} disintegration)* these limits become, in round figures, 40 and 100 percent, respectively, of the recommended maximum permissible level of $0.1 \mu\text{g Ra}^{226}$.

From these preliminary figures, therefore, we conclude that a more precise evaluation of skeletal activity in thorotrast patients is highly desirable. If these calculations are substantially correct, then this group of individuals (by virtue of its relatively large size, relatively long life expectancy and relative ease of access) should be regarded as an irreplaceable source of observational material eminently suited to complement the series of Ra^{226} patients reported in the literature. (22,23)

It should be borne in mind, however, that although these skeletal burdens would persist throughout the lifetime of the subject, they would not lead to the formation of "hotspots" as long lived as those present in the cases of Ra^{226} poisoning. In fact, the pattern of α -ray exposure in the thorotrast cases should not be too dissimilar to that present in the skeleton of populations ingesting Ra^{228} , Ra^{226} and Ra^{224} at or near natural levels since, essentially, they both result from continual intake.

*On the basis of 30% radon retention.

The activities involved, however, would differ by two to three orders of magnitude; hence, comparison of incidence of bone carcinogenesis in these two groups should throw some light on the validity of the claim, repeatedly ventured, that "spontaneous osteogenic sarcoma in humans is due to normal background radiation and that the incidence of the disease is directly proportional to the radiation dose to the skeleton."

TABLE E-I

Species	Organ	Elements	Time*	f	b (Skeletal)	Ref.	Remarks
Human	Liver	Ra ²²⁸ :Th ²³²	13.5-14.5 y	0.66		7	Thorotrast
	Spleen	Ra ²²⁸ :Th ²³²	13 y	0.74		7	Thorotrast
	Muscle	Ra ²²³ :Th ²²⁷	6 d	0.82		10	ThCl ₄
	Muscle	Ra ²²³ :Th ²²⁷	33-50 d	0.14		10	ThCl ₄
	Whole Body	Ra ²²⁴ :Th ²²⁸	20-230 d	0.88	0.06(f* = 0)	5	Thorotrast
	Whole Body	Ra ²²⁴ :Th ²²⁸	20-230 d	0.88	0.25(f* = .7)	5	Thorotrast
	Whole Body	Ra ²²⁴ :Th ²²⁸	20-230 d	0.88	0.50(f* = .82)	5	Thorotrast
	Whole Body	Ra ²²³ :Th ²²⁷	100 d	0.15	0.7 (f* = 0)	10	ThCl ₄
Dog	Carcass	Ra ²²⁴ :Th ²²⁸	10-100 d	0.60	0.2 (f* = 0)	8,9	Soluble Th

Note: The retentive factor f concerns the organ specified in the second column; the factors f* of the sixth column denote the retention factors of extra skeletal thorium deposits which would be lead to the observed whole body retention for the corresponding values of b.

*Time interval between thorium administration and observation.

F. APPENDIX

J. C. Reynolds

I. Exponential Approximation of the Chemical Retention Function

It is obvious that the power series expression for the chemical retention function $R_c(t)$ cannot hold for small values of t , for by definition $R_c(0) = 1$, while t^{-b} approaches infinity as t approaches zero. To circumvent this difficulty it is possible to approximate $R_c(t)$ by a sum of exponential series, matched to $R_c(0) = 1$ and to the power series for $t \geq 1$. Such an approximation would be continuous and would have continuous derivatives, and it would be easily integrable. In addition, it would have a certain amount of theoretical justification since the theoretical retention due to a finite number, n , of discrete and simple retaining compartments would be the sum of n exponential terms.

If the number of exponentials is finite, the approximation to the power series must be imperfect and must be limited to a finite interval of t . In this case the number of exponentials was arbitrarily set at four and the upper limit of the region of approximation at $t = 200$ days. Specifically, the approximation

$$R_c(t) \approx \sum_{i=1}^4 h_i e^{-a_i t}$$

was determined by the eight conditions

$$R_c(t) = 1 \quad \text{at } t = 0 \text{ days,}$$

$$R_c(t) = (1 - b) t^{-b} \quad \text{at } t = 2, 5, 10, 20, 40, 100, 200 \text{ days,}$$

giving eight equations for the eight unknown coefficients h_i and a_i .

The eight coefficients were calculated for $b = 0.1, 0.2, \dots, 0.8, 0.9$ by means of a relaxation procedure. An initial estimate was made of the coefficients, and successive estimates were produced by solving individual conditions for individual coefficients. This process was repeated cyclically until the convergence of successive sets of estimates indicated that the results were correct to within ± 1 in the third significant digit. Values of a_i and h_i are shown in the following table (F-I) and drawn in graphical form in the succeeding figure (F-1).

TABLE F-I
COEFFICIENTS OF EXPONENTIAL APPROXIMATION

b	h_1	h_2	h_3	h_4
0.1	0.596	0.138	0.126	0.140
0.2	0.352	0.179	0.199	0.270
0.3	0.206	0.171	0.230	0.393
0.4	0.118	0.142	0.232	0.507
0.5	0.0660	0.108	0.213	0.613
0.6	0.0354	0.0762	0.179	0.709
0.7	0.0179	0.0490	0.136	0.795
0.8	0.00801	0.0277	0.0920	0.872
0.9	0.00270	0.0128	0.0473	0.937

b	a_1	a_2	a_3	a_4
0.1	0.000595	0.0310	0.179	0.829
0.2	0.00119	0.0333	0.192	0.923
0.3	0.00184	0.0360	0.206	1.02
0.4	0.00246	0.0385	0.215	1.12
0.5	0.00311	0.0410	0.225	1.23
0.6	0.00378	0.0437	0.235	1.36
0.7	0.00444	0.0463	0.246	1.52
0.8	0.00509	0.0488	0.256	1.74
0.9	0.00585	0.0545	0.291	2.14

FIG. F-I: EXPONENTIAL COEFFICIENTS

II. Calculation of the Ra:Th Activity Ratio in Vivo. (Exponential Method)

The exponential approximation

$$R_c(t) = \sum_{i=1}^4 h_i e^{-a_i t}$$

may be substituted into the expression for the ratio $A(t)$ of radium activity to thorium activity. Since the exponential approximation for $R_c(t)$ is good within the range $0 \leq t \leq 200$ days, the resulting approximation for $A(t)$ will be good in the same interval. We have:

$$\begin{aligned} A(t) &= \lambda_R \int_0^t R_c(u) e^{-(\lambda_R - \lambda_T)u} du \\ &\approx \lambda_R \sum_{i=1}^4 \int_0^t h_i e^{-(a_i + \lambda_R - \lambda_T)u} du \\ &= \lambda_R \sum_{i=1}^4 \frac{h_i}{a_i + \lambda_R - \lambda_T} \left[1 - e^{-(a_i + \lambda_R - \lambda_T)t} \right]. \end{aligned}$$

This expression was evaluated for the three most important thorium-radium pairs, $\text{Th}^{227} - \text{Ra}^{223}$, $\text{Th}^{228} - \text{Ra}^{224}$, and $\text{Th}^{232} - \text{Ra}^{228}$. The following values of the daily decay rates were used:

Ra^{223}	.06188	Th^{227}	.03726
Ra^{224}	.1904	Th^{228}	.001
Ra^{228}	.0002834	Th^{232}	1.366×10^{-13}

Results are shown in the following tables (F-II, III and IV) and figures (F-2, 3 and 4).

TABLE F-II
ACTIVITY RATIO (EXPONENTIAL METHOD) $\text{Th}^{227} - \text{Ra}^{223}$

<u>t (days)</u>	<u>b = 0.1</u>	<u>b = 0.2</u>	<u>b = 0.3</u>	<u>b = 0.4</u>	<u>b = 0.5</u>
0	0	0	0	0	0
2	0.109	0.098	0.088	0.078	0.069
4	0.202	0.172	0.146	0.123	0.102
6	0.286	0.236	0.193	0.157	0.127
8	0.363	0.293	0.234	0.186	0.147
10	0.435	0.344	0.270	0.211	0.163
15	0.594	0.454	0.345	0.261	0.196
20	0.730	0.545	0.405	0.299	0.220
30	0.949	0.687	0.495	0.355	0.254
40	1.114	0.790	0.559	0.394	0.276
50	1.240	0.867	0.605	0.421	0.291
<u>t (days)</u>	<u>b = 0.6</u>	<u>b = 0.7</u>	<u>b = 0.8</u>	<u>b = 0.9</u>	
0	0	0	0	0	
2	0.060	0.051	0.043	0.033	
4	0.084	0.067	0.052	0.037	
6	0.101	0.078	0.058	0.039	
8	0.114	0.086	0.063	0.041	
10	0.124	0.092	0.066	0.043	
15	0.144	0.104	0.072	0.045	
20	0.159	0.112	0.076	0.046	
30	0.179	0.123	0.082	0.048	
40	0.191	0.130	0.085	0.050	
50	0.200	0.134	0.086	0.050	

TABLE F-III
ACTIVITY RATIO (EXPONENTIAL METHOD) $\text{Th}^{228} - \text{Ra}^{224}$

<u>t (days)</u>	<u>b = 0.1</u>	<u>b = 0.2</u>	<u>b = 0.3</u>	<u>b = 0.4</u>	<u>b = 0.5</u>
0	0	0	0	0	0
2	0.288	0.261	0.234	0.210	0.186
4	0.464	0.401	0.345	0.295	0.250
6	0.578	0.495	0.409	0.342	0.284
8	0.653	0.543	0.449	0.370	0.303
10	0.704	0.579	0.475	0.387	0.315
15	0.768	0.624	0.505	0.408	0.328
20	0.793	0.641	0.516	0.415	0.332
30	0.806	0.649	0.522	0.418	0.334
40	0.807	0.650	0.522	0.419	0.335
50	0.808	0.650	0.522	0.419	0.335
<u>t (days)</u>	<u>b = 0.6</u>	<u>b = 0.7</u>	<u>b = 0.8</u>	<u>b = 0.9</u>	
0	0	0	0	0	
2	0.164	0.141	0.118	0.092	
4	0.209	0.171	0.137	0.100	
6	0.232	0.186	0.145	0.104	
8	0.245	0.194	0.149	0.106	
10	0.252	0.198	0.152	0.107	
15	0.261	0.203	0.154	0.107	
20	0.263	0.204	0.155	0.108	
30	0.264	0.205	0.155	0.108	
40	0.265	0.205	0.155	0.108	
50	0.265	0.205	0.155	0.108	

TABLE F-IV
ACTIVITY RATIO (EXPONENTIAL METHOD) $\text{Th}^{232} - \text{Ra}^{228}$

t (days)	b = 0.1	b = 0.2	b = 0.3	b = 0.4	b = 0.5
0	0	0	0	0	0
5	0.00120	0.00102	0.00083	0.00068	0.00055
10	0.00226	0.00177	0.00138	0.00106	0.00082
15	0.00323	0.00244	0.00184	0.00137	0.00102
20	0.00417	0.00308	0.00226	0.00164	0.00119
30	0.00600	0.00427	0.00301	0.00211	0.00147
50	0.00952	0.00638	0.00432	0.00288	0.00192
70	0.01284	0.00842	0.00546	0.00353	0.00227
100	0.01765	0.01114	0.00699	0.00437	0.00273
150	0.02525	0.01538	0.00927	0.00558	0.00335
200	0.03248	0.01930	0.01128	0.00662	0.00387

t (days)	b = 0.6	b = 0.7	b = 0.8	b = 0.9
0	0	0	0	0
5	0.00044	0.00035	0.000262	0.000179
10	0.00062	0.00045	0.000320	0.000203
15	0.00074	0.00052	0.000358	0.000218
20	0.00084	0.00058	0.000386	0.000229
30	0.00101	0.00067	0.000430	0.000245
50	0.00125	0.00080	0.000490	0.000265
70	0.00144	0.00089	0.000531	0.000279
100	0.00167	0.00101	0.000578	0.000293
150	0.00198	0.00115	0.000638	0.000312
200	0.00223	0.00126	0.000682	0.000325

FIG. F-3: ACTIVITY RATIO $\text{Th}^{228} - \text{Ra}^{224}$ (Exponential Method) FIG. F-4: ACTIVITY RATIO $\text{Th}^{232} - \text{Ra}^{228}$ (Exponential Method)

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