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TRANSLOCATION OF THORIUM DAUGHTERS TO BONE*

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INTRODUCTION

ALTHOUGH evidence that thorium daughters separate from thorotrast deposits in humans has been sought before, it remained for Stenstrom[1] to establish in 1941 "that some elements of the thorium series were eliminated to a considerable extent from the tissues". In the postwar period both Rotblat *et al.*[2] and Rundo[3,4,5] reported results of more precise measurements on the radioactive equilibrium status of the thorium chain in liver, spleen and a few other tissues. Hursh *et al.*[6] in 1955 published detailed analysis of Th^{232} contents in several tissues, with some indications as to Th^{228} contents, and measured the excretion rate of the radium isotopes up to several months after injection. From these studies and various types of measurements at our laboratory,[7,8] sporadically described in our semiannual reports,[9,10,11] has emerged a rough picture of the physical and metabolic problems involved. The very attempt to a description of the phenomenon is hampered by the conflict entailed by the desirability of emphasizing simultaneously both the kinetics of metabolism and the relation between the volume of thorotrast injected and the absorbed radiation dose in various sites.

THE RADIOACTIVITY OF THE SKELETON

In this paper we shall concern ourselves principally with the radioactivity in the skeleton, referring only occasionally to the radioactivity of the active bone marrow which, potentially, may lead to greater tangible damage. We have gathered in Tables 1 and 2 all the known measurements of Th^{232}, Ra^{228} and Th^{228} made on human bone. Unfortunately, values for all three elements exist on only a few specimens. Hence, reference to contents at time of autopsy (*in vivo*) is strictly lacking in those instances in which considerable time elapsed between autopsy and analysis. The values shown have been obtained by extrapolating the radioactive content

* Work performed under the auspices of the U.S. Atomic Energy Commission.

of a given specimen to the whole skeleton* and by dividing this value by the radioactivity of the thorotrast injected, a ml of which contains 0·2 g or 0·022 μc of Th^{232}. The latter is not excreted by the human body in significant quantities,[6] and having a long half-life, it is essentially constant during the life of an individual.

The bone data have been separated into two tables to emphasize the necessity of distinguishing bone (*per se*) from bone not cleaned of marrow. The radioactive content of raw trabecular bone, as shown in Table 1, is conspicuously high and occasionally leads to absurd values. The only tenable explanation is that the bone enclosed marrow accumulates from the very beginning considerable thorotrast, and that the daughters Ra^{228} and Th^{228}, two decades after injection, are still present therein in quantities lower than expected from undisturbed radioactive growth, but considerably higher than expected from translocation (*vide infra*). In the two samples from which the values of three long-lived elements are available, there is sharp variation in the apparent equilibrium status of the chain. Sternum bone (Table 1, item 4), 20 years post injection, shows a much greater loss of daughters ($\sim 80\%$) than rib bone ($\sim 20\%$) one week after injection.† The values of Rotblat *et al.*[2] for the only two ratios of Th^{228} and Th^{232} reported in human marrow (12 years post injection) show losses of the order of 50%. We cannot say whether these values indicate that a slow change in "washout" takes place in the marrow. It is obvious, however, that to evaluate accurately the marrow dose, it is necessary to establish this trend carefully in as many patients as possible.

As far as bone is concerned, this time dependent increase in translocation of daughters from marrow will lead to increase in skeletal activity; however, if one considers that the marrow contains only about 10%[5] of the total Th^{232}, this increase should be small and negligible, to a first approximation at least.

* By assuming a weight of 7 kg for the skeleton and 2·8 kg for its ash. For patient 04-105 (Table 1), the body weight was known and the fresh skeleton weight was assumed to be 10% of it.

† As for the rib, R. E. Rowland of our laboratory has obtained positive chemical and autoradiographic evidence that the radioactivity was limited entirely to marrow. Hence, the absolute values obtained by extending the activity via the skeletal weight are not unexpectedly absurd in magnitude. The relative values of Th^{232}, Ra^{228} and Th^{228}, however, can be taken as representative of the marrow and deemed trustworthy because their actual proportions, both as actually injected and *in vivo*, were accurately measured, and extrapolation to full equilibrium in the injection was a matter of simple proportionality, involving no questionable assumptions.

TABLE 1

The Computed Activity of Th^{232}, Ra^{228} and Th^{228} in the Entire Skeleton as Obtained from Measurements of Samples of Fresh Trabecular Bone Containing Marrow. Activity of Injected Th^{232} = 100

Item	Patient code	Duration of burden	Specimen and weight	Time between biopsy analysis	Total skeletal activity as % of injected Th^{232}			Thorotrast injected cc	Method of analysis	Ref.
					Th^{232}	Ra^{228}	Th^{228}			
(1)	M.H.	17 d	Cancellous bone 97 mg ashed	—	6·0	—	—	75	Radiochemical	(6)
(2)	04-105*	9 d	Ribs 46 g fresh	3–300 d	(118)	(81)	(80)	48	γ-ray spectroscopy radioautograph	(9)
(3)	No. 2 (a)	15–20 y	Body of vertebra 12 g fresh	15 d	—	7·5	8·4	20	Radiochemical	(13)
	(b)		Head of femur 2·7 g fresh	180 d	—	2·9	2·6			
(4)	No.1 (a)	20 y	Sternum bone 1·41 g fresh	200 d	34·	6·7	5·9	60	Radiochemical	(13)
	(b)		1·35 g fresh	1·7 y	—	5·7	6·7			
(5)	A.D.	19 y	Cancellous bone 25 mg ash	—	26·4	—	—	75	Radiochemical	(6)

* Extrapolation to Th^{232} in equilibrium at injection (skeletal weight equals 10% body weight).

TABLE 2

The Computed Activity of Th^{232}, Ra^{228} *and* Th^{228} *in the Entire Skeleton as Obtained from Measurements of* ***Clean*** *Trabecular or Cortical Bone. Activity of Injected* $Th^{232} = 100$

Item	Patient code (age)	Duration of burden	Specimen and weight	Time between biopsy analysis	Total skeletal activity as % of injected Th^{232}			Thorotrast injected cc	Method of analysis	Ref.
					Th^{232}	Ra^{228}	Th^{228}			
(A)	04-101 (53)	18 y	Molar tooth 0·9 g ashed	350 d	0·50	—	1·68	10	Radiochemistry α-ray spectrometry	(10)
(B)	A.D. (a) (85) (b)	19 y	Compact bone 830 mg ash Trabecular bone 4·2 μg fresh	— 1 y	0·56 —	— —	— 1·74	75	Spectrochemistry Autoradiography	(6) (17)
(C)	M.H. (58)	17 d	Compact bone 20 mg ashed	—	0·56	—	—	75	Spectrochemistry	(6)
(D)	04-102 (a) (32) (b)	16 y	Vertebral bone 1·9 g ash 0·2 mg fresh	60–90 d	— —	5·5 —	4·2 3·7	(75)*	Radiochemistry Radioautography	(10) (7) (18)
(E)	04-104 (a) (75) (b) (c) (d)	26·5 y	Trabecular epiphysis tibia 4·9 g ash (B-3) Trabecular femur epiphysis 6·07 g ash (B-5) Cortical femur 3·04 g ash (B-6) Cortical femur 4·4 g ash (B-la)	zero zero zero zero	0·7 (0·7)* 0·40 (0·40)*	1·15 0·76 (063)* 0·63	1·11 1·04 0·80 0·76	10·	Radiochem. and α-spectromerty	(7) (8) (AA)
(F)	04-103 (a) (b) (37) (c)	15 y	Cortical femur 7·6 g fresh 5·4 g fresh vertebrae**	2·3 y 2·0 y 2.0 y	— — —	1·5 2·3 6·7	1·8 3·4 4·3	50	γ-ray spectrometry: high energy γ's low energy γ's	(AA) (14)

* Assumed values.
** Contaminated in jar by very active samples of liver and spleen.

TABLE 3

Retention of Th^{232} *Daughters in* R.E.S. *after Correction for Radioactive Growth*

For significance of L_1', L_2, L_3' and L_3 see text

Item	Patient code	Tissue (weight)	Duration of burden	Retention factors *in vivo*			Method of analysis	Ref.
				Ra^{228} L_1 or L_1'	Th^{228} L_2	Ra^{224} L_3 or L_3'		
(A)	No. 1	Liver (whole)	13·5 y	0·625	0·50	0·33	Growth of γ-activity	(3)
(B)	No. 2	Liver (whole)	14·5 y	0·62	0·45	0·30		
(C)	No. —	Spleen (whole)	13 y	0·69	0·57	0·43		
(D)	No. 1	Spleen (l.lg)	20 y	0·48	0·46	—	Radiochemistry and α-analysis	(13)
(E)	No. 2	Liver (43 g)	20 y	—	0·9 L_1	—	Radiochemistry and α-analysis	(13)
(F)	04-105 (a)	Liver (472 g)	9 d	0.56	0·78	—	γ-ray crystal spectrometry and growth of γ-activity	(9)
	04-105 (b)	Rib (46·2 g)	9 d	0·73	0·67	—		
(G)	04-103 (a)	Liver (24 g)	15 y	0·41	0·36	—	α- and γ-spectrometry, activity growth	(AA) (15)(14)
	04-103 (b)	Whole body	15 y	—	—	0·83 L_1	Crystal spectrometry	(14)
(H)	04-101	Whole body	18 y	0·63	$=L_1$	0·88 L_1	Crystal spectrometry	(11)
(I)	A.T.	Whole body	70–236 d	—	$=L_1$	0·88 L_1	Injection and excretion measurements	(6)
(L)	average 9 patients	Whole body	not specified	—	$=L_1$	0·78 L_1	Liquid scintillation counting	(16)
(M)	A.D.	Ten different tissues	19 y	—	0·46–0·75	—	Radiochemistry	(6)

The data concerning the radioactivity of specimen of trabecular bone cleaned with ethylenediamine or examined by radioautography to avoid the activity in the marrow, and of cortical bone (devoid of marrow) appear much more consistent (Table 2), despite the variety of methods of analysis employed.

Surprising, in a way, is the relatively small variation of the fraction of the Th^{232} in the skeleton. A question raised by item E in Table 2 is whether the difference in the Th^{232} contents of trabecular and cortical bone of a single subject (2-E) is due to normal anatomical factors or whether it is really a consequence of the atherosclerosis which led to the amputation of the limb. For the same reason, it is also impossible to show what relative values of Th^{232}, Ra^{228} and Th^{228} predominate in normal trabecular and compact bone. The higher values of Ra^{228} (and Th^{228}) in the younger patients, (2-D and 2-F), are in keeping with the greater avidity of the young skeleton for radium; they cannot be considered representative, however, inasmuch as values of washout from the R.E.S.* are not available for the first patient, and the washout in the second patient is greater than normal (*vide infra* and Table 3).

Worthy of note is the fact that Th^{228} is not always higher than Ra^{228}, and then by not much more than 30% (experimental error?) suggesting that translocated Th^{228} does not migrate *en masse* to the skeleton. It is more likely instead that this element is born in bone mineral from the decay of its parent Ra^{228}.

It is unfortunate that no data are now available about the presence of Ra^{224} and its short-lived daughters in the living skeleton of the thorotrast patient, for this element should be responsible for most of the dose in bone. To be reliable, this information will require proper handling of the specimen to avoid cross-contamination, and prompt analysis immediately after biopsy to establish the status of the shorter-lived daughters.

THE RADIOACTIVITY IN SOFT TISSUE

Although the contents of Th^{232} in a variety of tissues have been reported by Hursh,[6] and its retention in large fractions in the liver (70%) and spleen (7–20%) is well established,[5] the levels of its daughter products throughout the body is not clear.[12] Rundo [5] has measured the radioactivity of the blood (Pb^{212}, Ra^{224}) and the exhalation of thoron from the breath and has come to the conclusion that some thoron from the liver and spleen must reach the lung directly.

* R.E.S. = reticulo-endothelial system.

Fortunately, the data on the equilibrium of the main repositories of Th^{232} O_2 are more complete, though not abundant. In Table 3 we have gathered the pertinent results of Rundo,[3] Hursh[6,13] and those of our laboratory. In the table the letters L_1, L_2 and L_3 denote the fractions obtained by dividing the activities $\lambda_1 Ra^{228}$, $\lambda_2 Th^{228}$ and $\lambda_3 Ra^{224}$ in a given tissue (*in vivo*) by the corresponding activities that would obtain in a solution of Th^{232} (equal to that present in the tissue and initially devoid of all daughters) if it were sealed *in vitro* for an interval of time equal to the duration of the patient's burden. (See Eq. 3 below.) In what follows the factors pertaining to the body as a whole will be primed, i.e., L_1', L_3', etc.

The *in vitro* relative activities, t years after separation are computed as follows:

$$\begin{aligned} Th^{232} &= 1{\cdot}0 \\ Ra^{228} &= (1-e^{-\lambda_1 t}) = X \\ Th^{228} &= (1-1{\cdot}48\, e^{-\lambda_1 t}+0{\cdot}48\, e^{-\lambda_2 t}) = Y \end{aligned} \tag{1}$$

Ra^{224} may be considered in equilibrium with Th^{228} throughout the interval for which the patient is at risk.

In our calculations we have assumed:

$$\begin{aligned} \lambda_1(Ra^{228}) &= 3{\cdot}25\times 10^{-4}\ day^{-1}\ [19] \\ \lambda_2(Th^{228}) &= 1{\cdot}0\times 10^{-3}\ day^{-1} \\ \lambda_3(Ra^{224}) &= 0{\cdot}190\ day^{-1}. \end{aligned} \tag{2}$$

In Table 3 are included some miscellaneous values obtained from analysis of tissue specimens which may not be wholly representative of the entire organs from which they originated. Data obtained soon after injection (3-F), extrapolated to an injection in full radioactive equilibrium, confirms the absence of a true ionic fraction of Ra^{228} both in liver and in rib marrow, in agreement with the findings of Hursh *et al.*[6]

The value of L_1' in item 3-H is perhaps the only value available from whole-body measurements. It was obtained by measuring the Ra^{228} (actually Ac^{228}) by means of the intensity of the 900 keV γ-ray and by dividing it by the *known* Th^{232} injected.* The ratio L_1 should be essentially the same as L_1' because the skeleton contains only a few per cent of the Ra^{228} in the body (*vide infra*).

* Whole body measurements of patient 3-G did not yield L_1 because the amount of Th^{232} injected was not known. In fact the latter was estimated by the intensity of the 2·62 MeV γ-ray of Tl^{208} and the $Tl^{208}/Th^{232} = 0{\cdot}24$ in liver specimens.

The factor L_3' represents the ratio of activity of Ra^{224} (no growth correction necessary because of its short life) to that of Th^{232} for the body as a whole. Since whole-body measurements give essentially the $\lambda_3 Ra^{224}/\lambda_1 Ra^{228}$ (and Th^{228} is not excreted) it is evident that the latter ratio represents the ratio L_3'/L_1, when duly corrected for radioactive growth (see below). The assumption herein involved is that no daughters of Ra^{224} are lost from the body; experiments in humans[5] and animals[20] have shown that this can be considered true to a first approximation ($\sim 10\%$).

THEORETICAL CONSIDERATIONS ON TRANSLOCATIONS

A. *The Growth of Activity in Thorium-bearing Tissues*

Before entering into a comparison between the radioactivity of the various elements of the chain in liver and spleen (as repository of most of the thorium parent) and the activity found in bone samples and of the body as a whole on the basis of what is known about retention of soluble Ra^{226}, it is well to look into the "metabolic" meaning of the factors L as previously defined.

It is apparent that if we assume L_1, L_2 as constants and equal to:

$$L_1 = \frac{\lambda_1 Ra^{228}\ (in\ vivo)}{X \times \lambda_0 Th^{232}\ (\text{injected})}$$
$$L_2 = \frac{\lambda_2 Th^{228}\ (in\ vivo)}{Y \times \lambda_0 Th^{232}\ (\text{injected})} \qquad (3)$$

we are really assuming that in the R.E.S. the following differential equations hold:

$$\frac{d\,(Ra^{228})}{dt} = L_1\lambda_0 Th^{232} - \lambda_1 Ra^{228}$$
$$\frac{d\,(Th^{228})}{dt} = \frac{L_2}{L_1}\lambda_1 Ra^{228} - \lambda_2 Th^{228}. \qquad (4)$$

These expressions can be interpreted to indicate that a fraction L_1 of the Th^{232} atoms and a fraction $\frac{L_2}{L_1}$ of the Ra^{228} atoms disintegrating in the R.E.S. are retained therein, and that the rest are released to the circulation in time short compared to the half lives of the element in question.

The time-dependent behavior of the retentions R (Ra^{228}) and R (Th^{228}) in the R.E.S. system is easily evaluated by solving Eq. 4. If one assumes that only Th^{232} was injected, one obtains the following activities in the R.E.S.:

$$R(Ra^{228}) = L_1(1-e^{-\lambda_1 t}) = L_1 X$$

and

$$R\,(Th^{228}) = L_2(1-1{\cdot}48\ e^{-\lambda_1 t}+0{\cdot}48\ e^{-\lambda_2 t}) = L_2 Y \qquad (5)$$

when the Th^{232} activity—namely $\lambda_0\ Th^{232}$—is taken as unity and X and Y are as stated in Eq. 1.

The case of Ra^{224} needs special attention because its parent, Th^{228}, is translocated from the R.E.S. but it is not excreted from the body. This means that for the body as a whole the retention R' (Th^{228}) is given by:

$$R'\,(Th^{228}) = L_1 Y. \qquad (6)$$

The question arises as to whether the retained fraction of the Th^{228} atoms disintegrating in the body is the same everywhere, irrespective of the site of disintegration. If this is the case, the differential equation for Ra^{224} retained by the whole body can be written as:

$$\frac{d\,(Ra^{224})}{dt} = \frac{L_3'}{L_1'}\lambda_2 Th^{228} - \lambda_3\ Ra^{224} \qquad (7)$$

which means that a fraction L_3'/L_1 of the atoms of Ra^{224} born is retained *in situ*. This leads to the following value for the Ra^{224} retained by the body:

$$R'\,(Ra^{224}) \simeq L_3' Y. \qquad (8)$$

The value of L_3' can be calculated from the value of $L' = Ra^{224}/Ra^{228}$, observable by whole body counting. Obviously from Eq. (5) and (8)

$$L' = \frac{L_3' Y}{L_1 X},$$

and therefore:

$$L_3' = \frac{L'X}{Y} \cdot L_1. \qquad (9)$$

The values of L_3' entered in Table 3 have been calculated as per Eq. (9) whenever the burden time was known; otherwise X/Y was taken as unity.

B. *The Growth of Activity in the Skeleton*

The elimination and skeletal retention of a radium daughter released into the general circulation by an internally deposited thorium isotope has been the object of several studies which have led to the calculation of the skeletal retention function $A_n(t)$ and the elimination function $E_n(t)$

($n = 1$ for Ra^{228}, n = 2 for Th^{228} and $n = 3$ for Ra^{224}) for a number of radium daughters.[21,22]

For our purposes the retained fraction $R_c(t)$ of radium released is assumed to be:

$$R_c(0) = 1 \qquad (10)$$

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

Under these conditions the activity ratio $A(t)$ of the radium retained by the skeleton to the *effective* thorium releasing the daughter is given by:

$$A(t) = \frac{\lambda_R R(t)}{\lambda_T e^{-\lambda_T t}} = \lambda_r \int_o^t R_c(u) \cdot e^{-(\lambda_R - \lambda_T)\mu} du$$

and the elimination function, $E(t)$, namely, the daily rate of radium elimination divided by the effective thorium deposit, is given by:

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

Values of $A_1(t)$ for the Ra^{228}–Th^{232} combination have been plotted in Fig. 1 as a function of time for various values of b,* values $A_3(t = \infty)$ and $E_3(\infty)$ for the Ra^{224} and $E_1(\infty)$ for Ra^{228} are tabulated in Table 4.

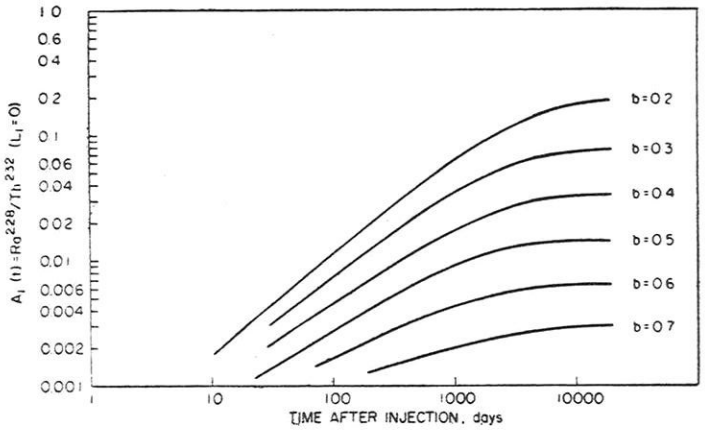

FIG. 1.

Activity ratio $A_1(t)$ describing the accumulation of Ra^{228} in the skeleton per unit activity of Th^{232} in the R.E.S. It is assumed that no Ra^{228} is retained in the R.E.S., that is $L_1 = 0$. Coefficient b refers to skeletal retention function $R_c(t) = (1-b)t^{-b}$. From Reynolds *et al.*[21]

* The reader should be reminded that in Reynolds *et al.* tables, the half-life of Ra^{228} was assumed to be 6·7 y instead of 5·8 y.[19] The values $A_1(t)$ for this isotope are, therefore, up to about 15% too low. This error is negligible for our purposes.

With these premises it is possible to proceed to some sort of comparison by summarizing in Table 5 some of the potentially observable quantities, such as skeletal retention and elimination rate, as functions of the "metabolic parameters" L and $A(t)$ of colloidal thorium and radium respectively. Before proceeding further it is necessary to consider the fate of Ra^{228} and Th^{228} injected with Th^{232}. The experimental evidence[6,2,9,5] indicates that the Ra^{228} injected with a thorotrast solution does not behave like "ionic" radium, since it is not excreted rapidly (only 20% of amount injected in about 8 days)[6] and it is found in the R.E.S. at 56% of the proportion

TABLE 4*

Activity Ratio $A_3(\infty)$ and Elimination Rates $E_3(\infty)$ and $E_1(\infty)$ for Various Values of the Exponent b

b	Ra^{224} $A_3(\infty)$	Ra^{224} $E_3(\infty)$	Ra^{228} $E_1(\infty)$
0·1	0·809	0·037	$1{\cdot}63\times10^{-4}$
0·2	0·651	0·067	2·32
0·3	0·524	0·091	2·61
0·4	0·419	0·111	2·74
0·5	0·333	0·127	2·80
0·6	0·261	0·141	2·82
0·7	0·200	0·153	2·82
0·8	0·147	0·163	2·82
0·9	0·101	0·171	2·84

* From Reynolds, *et al.*[21] The subscripts (1) and (3) refer to Ra^{228} and Ra^{224}, respectively. Times sufficiently long for equilibrium.

present in the injected material nine days after injection (item 3-F). The latter findings points to an elimination of 37% of the injected value in 9 days if the exponent in the skeletal $b = 0{\cdot}5$ (Eq. 10). In anticipation of a value of b less than 0·5, we may assume that Hursh's[6] and our findings are not incompatible in demonstrating that there exists a limited, but definite, amount of early washout of Ra^{228}. We shall assume as a maximum: (a), that the activity B of Ra^{228} in clinically injected thorotrast cannot possibly be greater than 44% of the activity of Th^{232} (thorotrast at most 5 years old), and (b), that 50% is retained in the bottle.[6,9] Hence, even if Ra^{228} were all ionic, it cannot possibly reach the skeleton in proportion greater than 22%.

If we assume $(1-L_1) = 0{\cdot}35$ as an average (Table 3), and assume $b = 0{\cdot}2$ (the lowest value found by Norris *et al.*[23] (for late Ra^{226} retention) we

TABLE 5

Summary of Retention and Kinetics of Th^{232} Daughters in the Body. Activity of Injected $Th^{232} = 1.0$

Element	R.E.S. retention	Skeletal retention (R)	Total body retention (R')	Daily rate "injected" in the circulation	Rate of formation	Daily elimination rate
Ra^{228}	$L_1 \cdot X$	$(1-L_1)A_1(t)$	$L_1 \cdot X - +(1-L_1)A_1(t)$	$\lambda_1 \cdot (1-L_1)$	λ_1	$(1-L_1) \cdot E_1(t)$
Th^{228}	$L_2 \cdot Y$	None	$L_1 \cdot Y + (1-L_1) \cdot A_2(t)$	$\lambda_2(L_1-L_2) \cdot X$	$\lambda_2 \cdot L_1 \cdot X$	0
Ra^{224}	$L_3 \cdot Y$	$[L_1-L_3] \cdot Y \cdot A_3(t)$	$L_3Y + (L_1-L_3) \cdot Y \cdot A_3(t) + (1-L_1)A_2(t)$	$\lambda_3(L_1-L_3) \cdot Y$	$\lambda_3 \cdot L_1 \cdot Y$	$[L_1-L_3] \cdot Y \cdot E_3(t)$

may calculate with the aid of Fig. 1 and Fig. 2 the maximum value of the Ra^{228} activity in the skeleton as:

Maximum skeletal $Ra^{228} = (1-L_1)A_1(t) + 0{\cdot}22 \times (1-0{\cdot}2)t^{-0{\cdot}2}\, e^{-\lambda_1 t}$

if the activity of Th^{232} injected is equal to unity.

This function, shown in Fig. 3, indicates that the value of Ra^{228} in the skeleton could be as high as 6 to 10% of that of the Th^{232} injected as early as 0·1 years and could be fairly constant from there on if $b = 0{\cdot}2$. However,

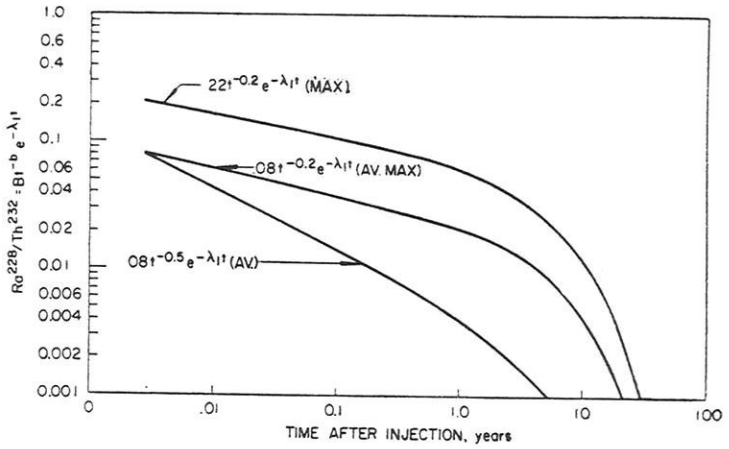

FIG. 2.

The retention of injected Ra^{228} (in units of Th^{232} activity) calculated for initial fractions B equal to 0·22 and 0·08 and for skeletal exponents $b = 0{\cdot}2$ and $b = 0{\cdot}5$.

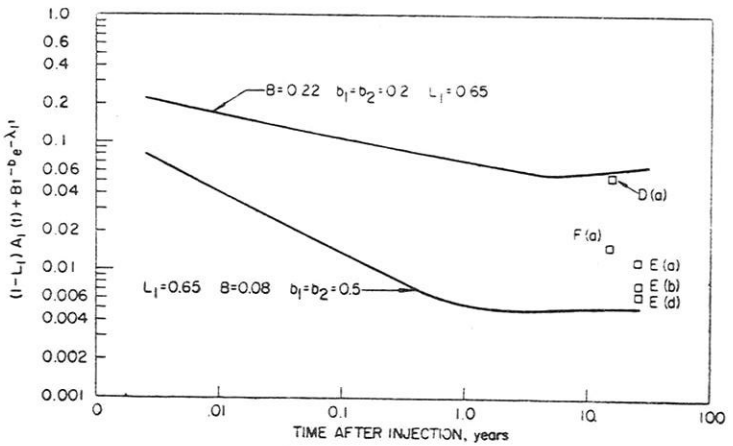

FIG. 3.

Calculated limits of skeletal Ra^{228} activity for average R.E.S. retention fraction $L_1 = 0{\cdot}65$ and parameters values: $0{\cdot}2 < b < 0{\cdot}5$ and $0{\cdot}08 < B < 0{\cdot}22$. Experimental points refer to items in Table 2.

a more realistic value from actual experience is $B = 0{\cdot}08$ and, for *externally* injected Ra^{226}, $b = 0{\cdot}5$. Assumption of these values leads to:

$$\text{Average } Ra^{228} \text{ skeletal value} = (1-L_1)\,A_1(t)+0{\cdot}08\times(1-0{\cdot}5)t^{-0.5} \quad (11)$$

represented by the lower curve in Fig. 3. The range delineated by these assumptions straddles the values found experimentally at $t > 15$ years, some of which are represented in the figure by the corresponding letters used in Table 2; experimental data are lacking at shorter times.

In these calculations we have assumed that the 0·5% of the injected Th^{232} found in the skeleton (Table 2) behaves—as far as retention of Ra^{228} and Th^{228}—as the rest in the R.E.S. That is to say, that its average contribution to skeletal Ra^{228} could not be much more than $0{\cdot}005\times L_1 = 0{\cdot}003$. This is a value large enough to push the lower limit slightly above some of the experimental points (atherosclerotic limb of patient 2-E) but still compatible with a reasonable value of b somewhat different from 0·5. This correction, however, is not sufficient to explain the higher bone values in the other patients. For case 2-F the high skeletal value is in part due to the lower retention in the R.E.S. (see 3-G) and hence a much lower value of b is not required.

As mentioned above, Th^{228} does not seem to migrate to bone mineral, hence it will not be discussed further in this paper.

Since no Ra^{224} measurements are available on bone itself, no direct comparison with experiment can be made. Some inferences, however, can be drawn with the aid of Tables 3, 4 and 5 and some comparison made between the *in vivo* ratios L_3' and L_3 and Hursh's observation of Ra^{224} elimination.

In Table 5 the reader will recognize the local activities of the various elements as derived in the previous discussions. Thus the Ra^{224} activity of the whole body is represented by the sum: (a) of the activity of the fraction L_3Y retained in R.E.S., (b) the skeletal activity due to translocation, and (c) the Ra^{224} born in the skeleton via Th^{232} and Ra^{228} — Th^{228} on the assumption that no translocation of Th^{228} and Ra^{224} takes place therefrom.

If, on the average, we assume that for the R.E.S., $L_1 = 0{\cdot}65$ and $L_3 = 0{\cdot}35$, and that for the skeleton $b = 0{\cdot}5$, then the activity of Ra^{224} in the whole body is:

$$R'(Ra^{224}) = (0{\cdot}35)Y+(0{\cdot}3\times Y\times 0{\cdot}333)+0{\cdot}008 = 0{\cdot}45Y+0{\cdot}008$$

and the activity of Ra^{228}

$$R'(Ra^{228}) = L_1X = 0{\cdot}65\,X.$$

Hence we calculate for $t \simeq 15$ years (Eq. 9):

$$L_3' = L'\,\frac{X}{Y}\,L_1 = \frac{0{\cdot}45\,Y\times 0{\cdot}008}{0{\cdot}65\,X}\cdot\frac{X}{Y}\cdot L_1 \simeq 0{\cdot}7.$$

This value is somewhat smaller than $L_3' \simeq 0{\cdot}83\,L_1$ observed experimentally (Table 3). Values of $b < 0{\cdot}5$ would increase these values of $A_3(t)$ in accord with the results of whole-body measurements, just as it would help explain higher Ra^{228} bone values discussed above.*

We may conclude, therefore, that in view of our scant knowledge concerning Ra retention at early times after injection, the predictions of the power law are satisfactory as a first approximation; these findings sustain the hope that the metabolic pattern in these patients may be found constant enough to justify the undertaking of a large international census[24,25,26] without incurring into too numerous whole-body γ-ray measurements nor into extensive (and expensive) analysis of body tissues and excreta.

SUMMARY

An attempt has been made to correlate the Th^{232}-Ra^{228} and Th^{228} values found in skeletal specimens of patients injected with known amounts of thorotrast with the radioactive equilibrium of the chain in the reticulo-endothelial system (R.E.S.).

The data for Ra^{228} are in accord with the predictions of Reynolds *et al.*[21] for values of the retention parameter $0{\cdot}2 < b < 0{\cdot}5$. No excess of skeletal Th^{228} is found to justify the assumption that "washout" Th^{228} translocates from the R.E.S. to bone mineral.

No data for actual Ra^{224} in bone are available, but whole-body and excreta activity measurements are consistent with the assumption that Ra^{224} is retained in the skeleton to a greater extent that Ra^{228}. Reliable direct measurements of this isotope are needed to establish with greater precision the chronic absorbed dose to the skeleton.

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* The activity of Ra^{224} in the skeleton $\simeq 0{\cdot}1\,Y$ supplies the bulk of the dose in the skeleton, hence it merits direct measurement. Further dosimetric consideration are to be found in ref. (21).

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DISCUSSION

WARREN: Using Dr. Faber's estimate of about 100,000 thorotrast-treated cases, there ought to be at least 1 case of osteogenic sarcoma in this large a population.

CHAIRMAN MARINELLI: We expect to see a few osteogenic sarcomas, in 2 or 3 years anyway.

DUDLEY: Perhaps the most useful practical data that can come out of the thorotrast work concern lung radiation dose rates because these dose rates are quite high. Observations of thorotrast patients may be helpful in evaluating the hazard to uranium miners, who are in fact breathing alpha emitters.

Rundo (*Phys. in Biol. & Med.* **3**, 101, 1958) found about 8% Tn^{220} (thoron) exhalation in thorotrast patients and we found the same in several patients measured at the Massachusetts Institute of Technology. Probably at least as much and quite likely more, Tn^{220} decays in the blood thereby giving rise to considerable Pb^{212} (thorium-B) and its subsequent daughters which will distribute in some pattern throughout the body. Who knows where they go? Is there any information as to whether these might localize in the skeleton?

FABER: Pb^{212} (thorium-B) tends to stick to red blood cells in animals breathing thoron. A member in our laboratory is working on this.

HURSH: We have recently injected four patients, each with 20 ml of thorotrast. So far the experiment is only half complete because we have only been able to make *in vivo* and excreta measurements (using a sodium iodide crystal γ-ray spectrometer). We have used Ac^{228} as an indicator for Ra^{228}, and Tl^{208} as an indicator for Ra^{224}. Measurements presently extend out to a year, and at least in some of our patients we will be able to follow them longer. For this early period our whole-body gamma measurements indicate that each day the patients excrete an amount of Ra^{228} equal to 90% of the daily Ra^{228} production and an amount of Ra^{224} equal to 40% of daily Ra^{224} production. In order to calculate these values, measurements of the "steady state" level of Ra^{228} and of Ra^{224} in the body were made. Since the amount injected is known (in one case, 0·614 μc Th^{232}, 0·16 μc Ra^{228}, 0·17 μc Th^{228} and 0·135 pc Ra^{224}) and since the measurements on man have shown that thorium is excreted to a negligible extent the rate of production and rate of decay of the nuclides are easily calculated and the rate of excretion arrived at. We will be interested in whether longer residence time in the body alters these excretion rates.