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Radium and Mesothorium Poisoning and Dosimetry and Instrumentation Techniques in Applied Radioactivity

10829287

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The Metabolism of Intravenously Administered Radium and Thorium in Human Beings and the Relative Absorption from the Human Gastrointestinal Tract of Radium and Thorium in Simulated Radium Dial Paints

1. Abstract

An experiment has been conducted to determine the relative absorption of thorium to radium from the gastrointestinal (G.I.) tract of normal human beings. This information is necessary in the interpretation of the toxicity data of Ra dial painters, a large number of whom ingested not only Ra^{226} but also Ra^{228} along with some fraction of an equilibrium amount of its daughter, Th^{228}. For use in toxicity correlations to date, the dosimetric equivalent of Ra^{228} has been expressed as a minimum pure Ra^{226} equivalent (MPRE) which presumes no dosimetric contribution from originally ingested Th^{228}.

Each of a group of elderly male and female human subjects was administered, intravenously, carrier-free Ra^{224} in saline or Th^{234} in isotonic citrate. Metabolic studies, conducted over a period of 21 days for Ra and 4 months for Th, include measurements on blood, urine, feces, and breath samples, and on the whole body and the upper 20% of the body with the gastrointestinal tract shielded, using a new so-called "skull and crossbones" (SXB) position.

The whole body retention of Ra decreases to ~15% in 20 days, while Ra in the total blood volume decreases to 0.3% in 4 days. The amount of Tn in the breath drops quickly in 2 days and decreases to 1.5% of the total Tn in 20 days. Radium is excreted predominantly by the fecal route, the feces-to-urine ratio averaging ~30. The crossover time (the time when the blood and skeletal specific activities are equal) is estimated to be ~75 days (range 40 to 150).

The whole body retention of Th is ~90% at 2 months, and decreases slowly, while Th in total blood decreases to ~0.3% in 10 days. Th is excreted mainly through the urinary route, the urine-to-feces ratio averaging ~10 for males and ~20 for females. The shielded SXB measurements indicate a disproportionately smaller amount of Th in the upper ~20% of the body for males than for females. The reasons for these two sex differences in the metabolism of Th are unknown.

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Each of a second group of elderly male and female normal human subjects was administered, orally, a gelatin capsule containing simulated Ra dial paint consisting of Ra^{224} SO_4, Th^{234} $(SO_4)_2$, and $BaSO_4$ carrier deposited on ZnS phosphor to simulate the original Ra dial paints. The transport of Ra and Th across the gut wall was determined by the same measurements described above which provided calibration data for this phase of the experiment. All methods of measurement are necessary because of the expected low Th absorption and of the great possibility for contamination.

The results indicate a transport of 15-20% of the Ra across the gut wall. This value is unexpectedly high, comparable with that of Ra from drinking water. The detection of the transport of Th is borderline, corresponding to ~0.1% that of Ra within a factor of 2. It is concluded that the absorption of Th^{228} (in equilibrium with its parent Ra^{228}) from real dial paints is unlikely to have been high when dial painters tipped their brushes in the 1920's. Therefore, in these dial painters the contribution to the integrated radiation dose by the initially absorbed Th^{228} is $\leq 5\%$ that due to Ra^{228}.

On the basis of these absorption results, the use of "minimum" in the concept of pure Ra equivalent is no longer necessary and all toxicity correlations can be evaluated in terms of pure Ra equivalent (PRE).

2. Summary and Conclusions

1. The purpose of this study was to determine the potential importance of Th^{228} in the internal dosimetry of Ra^{228} ingested by Ra dial painters. The experiment was conducted by administering short-lived isotopes of Ra and Th to human beings. The calibration data were obtained by a separate experiment involving the intravenous administration of short-lived Ra and Th, providing additional information on the metabolism of Ra and Th by human beings.

2. Methods for the separation, purification, preparation, and standardization of Ra^{224} and Th^{234} are described. Carrier-free preparations are made using ion-exchange procedures. Millicurie amounts of Th^{234} are separated from slag obtained from uranium melts. Procedures are described for the preparation of pyrogen-free sterile Ra^{224} and Th^{234} solutions for intravenous injections. A procedure for making

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3. Analytical techniques include measurements on blood, breath, urine, and feces samples, all of which are described. Whole-body measurements are made using an arc method for absolute measurements and the standard chair method. A new method is described, the so-called "skull and crossbeam" (SXB) technique, in which the upper ~20% of the body is exposed to the detector while the remainder is shielded with Pb to provide an attenuation of $\sim 10^{-3} - 10^{-4}$ for 2.61-MeV gamma rays arising from anywhere in the human G.I. tract below the level of the top of the stomach.

4. The human subjects for this study were normal males and females with an age range of 63 to 83 years. These individuals were selected on the basis of a detailed medical history and a detailed clinical evaluation. In particular, there was no evidence of significant endocrine, gastrointestinal, or skeletal disorders.

5. Following intravenous injections, Ra^{224} decreases rapidly in blood to $\sim 10^{-2}$ the value at t = 0 in ~5 days. Whole-body retention is 15% at 20 days. During this observation period Ra retention is ~1.5 times greater than that predicted by the Norris, et al., power function but the experimental values appear to be converging to this power function. Fecal excretion is the primary route of excretion with the fecal-to-urine ratio = ~30. Ten percent of the initial total Tn produced in the body is found in the breath immediately after the Ra^{224} administration and this value reduces to 0.3% in ~20 days. The Tn in the breath expressed as a percent of the retained Ra^{224} decreases to ~1.5% in ~20 days, a value 10 times greater than the value found in subjects with long-term burdens of Ra^{228}. The crossover time (the time when the blood and whole body specific activities are equal) is ~75 days (range 40-150 days). The calibration experiments indicate that the arc method of determining whole-body Ra burden is accurate within about ±5%. The fraction of the Ra^{224} body burden determined by the SXB measurement is ~40% of that of long-term Ra^{226} burdens, and this difference is explainable in terms of the Ra^{224} content of soft tissue and of the lower G.I. tract (marked for excretion) at times relatively soon after administration. The results showed no significant dependence on sex.

6. Following intravenous injection, Th^{234} decreases more slowly than Ra in blood, to 0.3% the value at t = 0 at ~10 days. Whole-body retention decreases to ~92% in ~5 days and decreases very slowly over the ~110-day observation period (range of biological $T_{1/2}$ = 2 years to ∞).

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Urinary excretion is the primary route of excretion with the feces-to-urine ratio = ~0.03 for males and ~0.04 for females. The calibration experiments indicate that the arc method of determining whole-body Th burden is accurate to ~±15% but with some indication of a trend. The fractions of the Th^{234} body burdens observed with the SMD measurements are constant over a 2-month period but are different for males and females. The differences in body Th distribution and in excretion observed between the sexes is a new observation but remains unexplained.

7. The experiment on the relative absorption of Ra and Th was conducted by administering to each of a group of subjects simulated Ra dial paint consisting of Ra^{224} SO_4, Th^{234} $(SO_4)_2$, and $BaSO_4$ in a matrix of ZnS phosphor, all contained in a gelatin capsule. With both nuclides given at the same time, each subject served as his own control. Transport across the gut wall was determined by all the measurements described for the intravenous studies because of the expected low transport of Th^{234} and of the great potential for contamination. Transport is calculated from the data obtained long after the transient effects of the absorption process have become negligible.

8. The transport by human beings of Ra^{224} from such simulated Ra dial paint was found to be ~20% for both sexes (excluding one male who showed ~1% transport and who was later found to have achlorhydria). This value is comparable with that for drinking water. The amounts estimated to have been eaten by dial workers and the resulting body burdens observed many years later are not inconsistent with this value.

9. The transport of Th^{234} under the same conditions was found to be on the borderline of detectability and equal to ~0.1% that of Ra^{224} within a factor of ~2.

10. With this low value of the relative absorption of Th to Ra, it can be concluded that the internal radiation dose from ingested Th^{228}, when present in equilibrium with its parent Ra^{228} in Ra dial paint, is ≤ 5% that of Ra^{228}.

11. In the study of Ra toxicity cases at M.I.T. many subjects had ingested both Ra^{226} and Ra^{228}. For purposes of assessing the clinical findings with the combined effect of these two nuclides, a unit of minimum pure Ra equivalent (MPRE) has been used by which the dosimetric contribution of Ra^{228} is converted to an equivalent quantity of Ra^{226}. The use of the word minimum was used to indicate the unknown, if any, contribution to the Ra^{228} dose by the original Th^{228} present in the paint. [illegible] basis of the present results, the Th^{228} can be neglected and the

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dosimetric equivalent of Ra^{223} can now be expressed as a pure Ra equivalent (PRE).

3. The Comparative Metabolism and Absorption of Radium and Thorium in Human Beings

For those concerned with the health problems involving ionizing radiations, the effects in living tissues of Ra^{226} and its daughter products have comprised a "bench mark" of radiobiological measure on which has been based much of the thinking relating to protection standards for internal emitters over the past two decades. Beginning with the observation of "radium jaw" in dial painters first reported by Blum[1] which was soon followed by the now classic reports published by Martland[2,3], there has emerged a series of long-term studies[4,5] detailing the variety of effects due to Ra and MsTh. Among the notable changes have been necrosis of the jaw, aplastic anemias, and the development of osteogenic sarcomas, often in conjunction with spontaneous pathologic fractures of the bones.

It is known that the dial paint contained Ra^{226} or a mixture of Ra^{226} and its isotope, Ra^{223} (MsTh) usually in partial equilibrium with its daughter product, Th^{228} (radiothorium, RdTh). In the dial painting performed in Waterbury, Connecticut, for example, the painters used a mixture containing both these isotopes of Ra. The radiation dosimetry and toxicity in these individuals would thus be markedly different from those who worked with paints containing Ra^{226} alone.

The problems attendant to the fact that mixtures of isotopes were used in dial paints have been reviewed in some detail[4]. After taking

1. T. Blum, "Osteomyelitis of the Mandible and Maxilla", J. Am. Dental Assoc., 11, 802-805 (1924).
2. H.S. Martland, P. Conlon, and J.D. Knef, "Some Unrecognized Dangers in the Use and the Handling of Radioactive Substances, with Especial Reference to the Storage of Insoluble Products of Radium and Mesothorium in the Reticular and Endothelial System", J. Am. Med. Assoc. 85, 1769-1776 (1925).
3. H.S. Martland, "The Occurrence of Malignancy in Radioactive Persons", Am. J. Cancer 15, 2435-2516 (1931).
4. J.C. Aub, R.D. Evans, L.H. Hempelmann, and H.S. Martland, "The Late Effects of Internally-Deposited Radioactive Materials in Man", Medicine 31, 221-329 (1952).
5. R.J. Easterlik, "The Delayed Toxicity of Radium Deposited in the Skeleton of Human Beings", Proc. International Conference on Peaceful Uses of Atomic Energy, Geneva, 1955, 2, 149-155 (1955).

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into consideration the physical and metabolic properties of Th^{228}, Ra^{226}, their daughter products, their half-periods as well as their alpha energies, it can be calculated that Th^{228} delivers ~20 times the total dose to bone that Ra^{226} does. Based on equivalent microcurie retention, comparative toxicity studies in dogs and mice[6,7], have in general supported this rad dose difference in that equivalent amounts of Th^{228} and Ra^{226} retained by bone results in about a 5-fold or greater incidence of bone tumors or lethality in the animals injected with Th^{228}

For some time it has been of great interest to determine to what extent any Th^{228} originally present in dial paints may have contributed to the radiation bone dose experienced by dial painters. Not only was there Th^{228} present in dial paints due to ingrowth from Ra^{228}; but in some instances Th^{228} was added along with Ra^{226} and Ra^{228}. Present day measurements of Th^{228} in the bones of former dial painters are due to the parent Ra^{228} which was originally deposited, since any Th^{228} ($T_{1/2}$ = 1.9 years) (see Figs. 71 and 72, decay schemes for Ra^{226}, Ra^{228}, Th^{234}) originally ingested by dial painters would long since have decayed away. It is obvious that to establish the uptake and retention of Th relative to that of Ra would require a metabolic study carried out under more-or-less original dial painter conditions. Such an experiment was proposed by Evans[8] and later detailed more specifically by Dudley[9].

It has been apparent that extrapolations from animal data would not be completely satisfactory since experiments at the University of Utah[10]

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6. T. Dougherty, "Incidence of Bone Cancer in Internally Irradiated Dogs", in Some Aspects of Internal Irradiation, ed. T. Dougherty, pp. 47-61, Pergamon Press, 1962.

7. M.P. Finkel, "Relative Biological Effectiveness of Internal Emitters", Radiology 67, 665-672 (1956).

8. R.D. Evans, in Second Annual Conf. on Plutonium, Radium, and Mesothorium, Salt Lake City, Utah, ed., C.N. Stover, Jr., June 17-19, 1954, p. 67.

9. R.A. Dudley, "Thorium and Radium Uptake from Human Gut. Proposed Investigation", M.I.T. Radioactivity Center, Progress Report, pp. 114-117 (May 1950).

10. D.R. Atherton, B.J. Stover, M.H. Van Dilla, "Absorption of Radium and Thorium Through the Gut as a Function of Chemical Form, IV", Semiannual Progress Report, Radiobiology Laboratory, University of Utah, pp. 91-93 (Sept. 1957).

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demonstrated that, while Th is absorbed less than Ra most of the time, the absorption of Th could be greater than that of Ra depending on chemical form or animal species studied.

Broadly speaking, those studies on human subjects which have been reported reflect the findings in animals, particularly those studies with reference to the metabolism of soluble Ra salts[11,12]. In general, for both human beings and animals, following the initial rapid clearance from the body, injected Ra tends to be eliminated slowly, the total body retention decreasing to ~0.1%-1% in a 30 to 40-year period for human beings.

In the case of Th the retention is high with an apparent long biological half-period[13]. Although some information about the metabolism of Th and its daughter products following injection of Thorotrast is available[14], to best of our knowledge no direct experimental information about the absorption of Th salts in human beings has been reported.

Indirect evidence has indicated that Th is poorly absorbed from the human G.I. tract[15]. Briefly, it has been reported that while Ra^{226}, Ra^{228}, and Th^{228} are present in the human body, Th^{232} is not found or is low[16,17]. This has given rise to the supposition that the Th^{228} originates

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11. H.A. Seil, C.H. Viol, and M.A. Gordon, "The Elimination of Soluble Radium Salts Taken Intravenously and per os", N.Y. Med. J. 101, 896-898 (1915) or Radium 5, 40-44 (1915).

12. W.P. Norris, T.W. Speckman, and P.F. Gustafson, "Studies of the Metabolism of Radium in Man", Am. J. Roentgol. Radium Therapy Nucl. Med. 73, 785-802 (1955).

13. B.J. Stover, D.R. Atherton, N. Keller, and D.S. Buster, "Metabolism of the Th^{228} Decay Series in Adult Beagle Dogs. I. Th^{228} (RdTh)", Radiation Res. 12, 657-671 (1960).

14. J.B. Hursh, L.T. Steadman, W.B. Looney, and M. Colodzin, "The Excretion of Thorium and Thorium Daughters after Thorotrast Administration to Human Subjects". Acta Radiol. 47, 481-498 (1957).

15. W.V. Mayneord, J.M. Radley, and R.C. Turner, "The Alpha-ray Activity of Humans and Their Environment", Proc. Second Internat. Conf. on Peaceful Uses of Atomic Energy, 23, 150-155 (1958).

16. C.R. Hill, "Identification of α-emitters in Normal Biological Materials", Health Phys. 8, 17-25 (1962).

17. A.H. Stehney, "Radioisotopes in the Skeleton: Naturally Occurring Radioisotopes in Man", Radioisotopes in the Biosphere, R. S. Caldecott and L.A. Snyder, eds. University of Minnesota Press, pp. 366-381, 1960.

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from the metabolic uptake of Ra^{228}. Up to the present, however, adequate quantitative data on the relative absorption of Ra and Th from the human G.I. tract have not been available.

The studies reported in this paper represent an effort to answer the question of whether or not Th^{228} present in dial paints makes an important contribution to bone radiation dose. Assuming equilibrium existed, many of the dial painters ingested microcurie amounts of Th^{228} comparable with those of Ra^{226} and Ra^{228}. With a total rad dose from Th 20 times that of Ra^{226} for equal activities absorbed, it was arbitrarily decided that if our studies showed the uptake of Th to be $\leq 10^{-2}$ that of Ra then the dose contribution of the Th^{228} in dial painters could, for all practical purposes, be disregarded. In fact, such a result would change our present concept of MPRE* to PRE, thereby dosimetrically accounting only for the effects of Ra^{226} and Ra^{228}, and in effect disregarding any potential Th^{228} bone-dose contribution implied by the MPRE concept. In what follows it will be shown that the fractional uptake of Th from the G.I. tract is indeed small, and that relative to Ra^{228} it would not appear to make an important bone-dose contribution. As such, the question of the possible toxicity of Th^{228} originally present in dial paints would appear to have

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*MPRE = minimum pure Ra equivalent. In those individuals who ingested both Ra^{228} and Ra^{226}, one can measure the current body burden of each of these isotopes. Knowing when the exposure occurred, as well as the physical characteristics and metabolism of the nuclides, one can calculate the initial retained body burden for each of these two nuclides. Since in those instances when Th^{228} was also ingested (which very likely was every instance for mixtures of Ra^{228} and Ra^{226}), the amount of Th^{228} taken up and retained was unknown, the bone dose which was calculable (on the basis of present-day measurements) was only that delivered by Ra^{226} and Ra^{228}. In this sense this was the "minimum" bone dose that must have been delivered, inasmuch as there was no way to account for Th^{228}. The MPRE has, therefore, been defined as that amount of Ra^{226} which will deliver the same total rad dose as any given mixture of Ra^{226} and Ra^{228} currently found in the body. The definition of MPRE is given by the following equation:

$$\text{MPRE} = \left[1 + \begin{pmatrix}\text{Present}\\ Ra^{228}/Ra^{226}\\ \text{Ratio}\end{pmatrix}\begin{pmatrix}\text{Ra-228}\\ \text{decay since}\\ \text{first exposure}\end{pmatrix}\begin{pmatrix}\text{Ratio of}\\ Ra^{228}/Ra^{226}\\ \text{rads}/\mu\text{Ci}/\text{rads}/\mu\text{Ci}\end{pmatrix}\right] Ra^{226}\ \mu\text{Ci}$$

Illustration for dial painters from Waterbury, Connecticut
MPRE = 1 + (0.053) (100) (1.5) = 10.5 μCi Ra^{226} (18).

18. C.J. Maletskos, A.G. Braun, M.M. Shanchan, and R.D. Evans, "Quantitative Evaluation of Dose-Response Relationships in Human Beings with Skeletal Burdens of Ra^{226} and Ra^{228}", in "Assessment of Radioactivity in Man", pp. 225-251, IAEA, Vienna, 1964.

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been resolved, in a sense thus reaffirming the judgments on which the present maximum permissible body burden for Ra^{226} were based.

It is perhaps pertinent to point out that these conclusions are warranted only on the basis of the conditions under which the experiments were conducted, and that extrapolations about relative Th toxicity have been made on this basis. Thus, while the experiments approach the dial painters' circumstances, in that an attempt was made to duplicate dial painter ingestion conditions, they may, in fact, not fully reflect the true situation.

Both males and females were studied. Older individuals were used as study subjects, while the dial painters were actually young females, very often still in their late teens.

The methods of whole-body counting as well as excretion analysis were used. The isotopes of Ra and Th used were Ra^{224} and Th^{234}. These isotopes were chosen after considering both radiometric as well as dosimetric problems which might be encountered[9]. In the process of obtaining calibration data, the intravenous metabolism of these two isotopes was studied and these additional results are also included in the report.

4. Materials and Methods

a. Separation, purification, and preparation of Ra^{224} and Th^{234} for intravenous and oral administration.

This section describes the procedures for the separation, purification, and preparation of Ra^{224} and Th^{234} for intravenous injection and for oral administration, for the conditioning of the ion-exchange column for pyrogen-free applications, and for the preparation of mock Ra paint containing both Ra^{224} and Th^{234}.

The short half-period of Ra^{224}, the difficulty of making a good Th^{234} separation, the 10-day waiting period for the bacterial and pyrogen tests, the disturbance of the radioactive equilibrium between the parents, Ra^{224} and Th^{234}, and their respective daughters during the radiochemical and other preparatory operations, all tend to make the procedures for the preparation and administration of these isotopes more complicated than they may appear. Careful logistics are needed to synchronize all the steps of the procedures and at certain points the steps are taken blindly with the expectation that they will work, i.e., analytical checks are not carried out necessarily at every step.

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(C) Preparation of mock Ra paint.

Mock Ra paint for oral administration was made to contain both Ra^{224} and Th^{234}. The preparation of this mock paint follows the basic plan described by the Radiobiology Laboratory at the University of Utah[25] which in turn is based on information supplied by Mr. C. W. Walhausen of the U. S. Radium Corporation. The commercial dial paints manufactured during the post-World War I period had a variable composition from time to time so that any paint prepared today would only approximate the old paints. The dial paint prepared by the Utah group is a well-defined reproducible paint free of soluble activities and serves as a useful reference.

The difference between the procedure to be described and that of the Utah group is related to the short half-periods of the isotopes used for this experiment compared with the long half-periods of isotopes used (Ra^{226} and Th^{228}) by that group. Accordingly, the present procedure is used to make enough paint for administration to one person.

Fifty mg ZnS phosphor, type G-121,* are placed in a conical polyethylene centrifuge tube and 0.5 ml 3.6×10^{-4} M $BaCl_2$ carrier is added. Ra^{224} in ~0.5M HNO_3 and Th^{234} in ~0.5M HCl are added in such a way that their combined volume does not exceed 3-4 ml. If necessary, distilled H_2O is added to bring the volume to 3-4 ml. The pH is adjusted to 3 - 4.5 with 1M and 0.1M NaOH using universal pH paper. One-half ml 7.2×10^{-4} M $(NH_4)_2SO_4$ is added while stirring the slurry to precipitate the Ra and to adsorb the Th. One-quarter ml 3.6×10^{-4} M $BaCl_2$ is added as extra

25. B.J. Stover, D.R. Atherton, and M.A. Van Dilla, "Absorption of Thorium and Radium through the Gut. Effect of Chemical Form", ANCU-3418, pp. 14-16 (March 1955).

* Similar to the phosphor used in the post-World War I era and obtained from the U.S. Radium Corporation.

The percentage composition of the ZnS phosphor, >200 mesh, is shown below. Zn and S were determined chemically while the other elements were analyzed spectroscopically. Note that Th is present in the phosphor corresponding to < 15 μg Th^{232} per capsule of 50 mg phosphor. The Th^{232} can be as much as ~2000 times greater than the ~8.6 ng Th^{234} administered (~200 μCi). The Th^{228} or Ra^{224} activity contributed by this amount of Th^{232} in the mock paint is ≲1.7 pc and is trivial compared with the detection sensitivity for the body measurements of Ra^{224}. Gamma measurements on the ZnS phosphor placed in a clean polyethylene container showed <100 pc Ra^{226}/g phosphor, an amount which is also trivial.

Zn 66.1, S 32.6, Hg < 0.01, Mn < 0.001, As < 0.001, B ~0.01, Sb < 0.001, Bi < 0.001, Cu 0.003-0.03, Tl < 0.01, Th < 0.03.

carrier and 0.1 ml 7.2×10^{-2}M $(NH_4)_2CO_4$ is added as excess $CO_4^{=}$ to force a maximum precipitation and adsorption onto the phosphor particles. The final volume is ~9 ml (or is adjusted to this volume with additional distilled H_2O) and the pH is still ~4.

After ~10 min. the slurry is centrifuged and the supernate is removed with a capillary pipet. The centrifugation and removal of supernate are repeated three times with 3-ml aliquots of distilled H_2O and twice with 2-ml aliquots of acetone. Enough acetone is left from the last wash so that a heavy slurry can be made. The slurry is transferred with a capillary pipet to the smaller half of a No. 3 gelatin capsule (held in styrofoam), the phosphor settles quickly, and the excess acetone is returned to the centrifuge tube. The procedure is repeated until the transfer of the phosphor is complete. The acetone is allowed to evaporate from the capsule until the phosphor is damp (do not take to dryness because the product is very powdery). The capsule is sealed by wetting the upper outer surface of this smaller half of the capsule using a brush moistened with water and quickly pushing on the larger or top half. Overnight, the remaining acetone diffuses out and the paint is powder dry. As a precaution, this capsule is stored in a larger No. 1 gelatin capsule and sealed in a polyethylene vial for standardization prior to administration.

The radioactive yields of the mock paint are not completely predictable. The Ra^{224} yield averages 50%, range 5-80%, while the Th^{234} yield averages 50%, range 30-60%.

b. Standardization and physical characteristics of Ra^{224} and Th^{234}.

Standardization of Ra^{224} for purposes of administration to human subjects is carried out against a sample of $Th(NO_3)_4 \cdot 5H_2O$ of known pedigree and weight and contained in a glass ampoule. The standard is greater than 40 years old so that there is secular equilibrium between the Th^{232} and its daughters. The activity of the Th^{232} standard is based on its half-period, taken to be 1.40×10^{10} years[26,27].

A simplified decay scheme of Th^{232}, including Ra^{224} and its daughters and containing the information pertinent to this study, is shown in Fig.71.

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26. D. Strominger, J.M. Hollander, and G.T. Seaborg, "Table of Isotopes", Rev. Mod. Phys. 30, 812, (1958).

27. T.A. Farley, "Half-period of Th^{232}", Can. J. Phys. 39, 1059-1068, (1961).

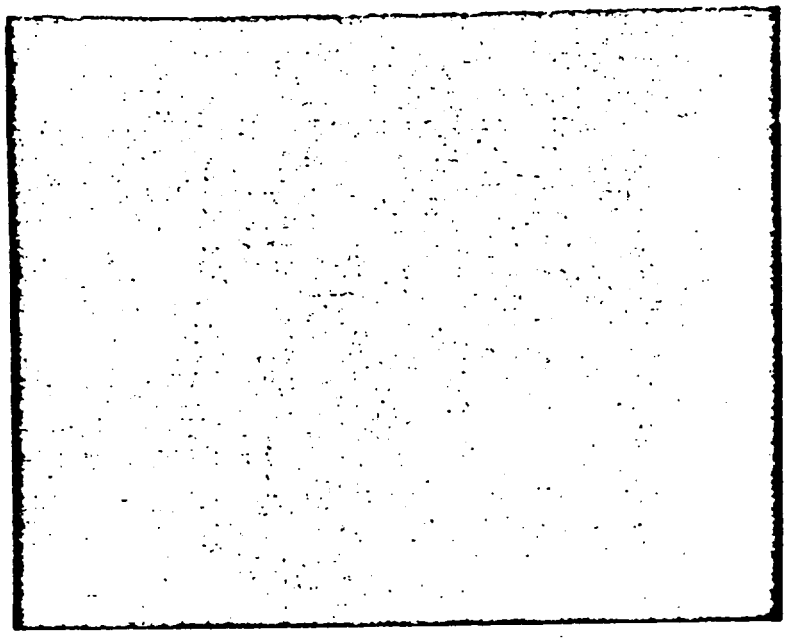

FIG. 74. Pb SHIELD - CRYSTAL CONFIGURATION FOR S X B MEASUREMENTS

FIG. 75. SUBJECT IN S X B POSITION

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corresponding to the center of the head, gives a counting rate of $\sim 10^4$ cpm/μCi or $\sim 2 \times 10^3$ cpm/μCi contained in the whole body, where ~20% of the body is seen by the detector. This compares well with the value of $\sim 2.6 \times 10^3$ cpm/μCi given in Table 31 on human subjects. The phantom measurements are sufficiently close to reality to allow some predictions of sensitivity and calibration.

Using a minimum detectable counting rate of 3 cpm in the 2.61-MeV region and ~16 cpm in the 1.00-MeV region, the results of Tables 32 and 33 are summarized in Table 34.*

Two gain settings on the multichannel analyzer have been used for the most effective resolution of the high-energy or low-energy γ rays. The designations for these two calibrations for the SXB position are H8SXB and L8SXB, the H and L for high and low energy and the 8 for the 8" x 4" crystal to distinguish these measurements from other such measurements with other crystals.

The results show that the SXB position can meet the sensitivity requirements of the study. In particular, the contribution to the SXB signal from residual activity in the G.I. tract which can only be interpreted as a body burden is less than the minimum detectable activity per μc in the G.I. tract.

Table 35 shows the anticipated doses required for detection of various fractional uptakes from the G.I. tract. These are calculated using the results of Table 34 for the conditions where the subject's normal activity, the subject's administered activity, and room background are counted for 30 min. each.**

On the basis of these phantom calibration studies, the SXB position was judged satisfactory and a final shield was constructed as shown in Figs. 74 and 75. A steel angle-iron dolly is constructed sturdily to hold

*During the Th^{234} phantom measurements, it became apparent that the sensitivity could be increased by a factor of ~10 using the 64- and 93-keV γ rays of Th^{234}. Because the phantom is not too representative of the human body at these low γ-ray energies, these phantom measurements were not carried out but were left to be made during the intravenous studies on the human subjects. Estimated values for these energies are included in Table 34.

the 600-700 lb. lead arrangement described for Fig. 73. The dolly has large casters for convenience in rolling it in and out of the whole-body counter, in this case on a track to accommodate the 6" rise into the room. The Pb bricks are housed in an angle-iron and masonite form on a plywood dolly top reinforced with angle-iron below. The subject sits on a cushioned adjustable-height drafting chair with a back rest. The chair is drawn up until the subject's chest is snug against the shield and the chair is secured. The chair height is adjusted so that the chin rests on the top Pb brick with the forehead against a styrofoam block to set the distance of 2-1/2" between the mesion and crystal face The arms are then placed comfortably around the top of the Pb shield an around the crystal, with styrofoam blocks supporting the elbows, as sho in Fig. 75.

When large amounts of activity are in the G.I. tract, scattered radiation of low energy and the ~72-keV Pb fluorescence x-ray cause hi counting rates in the energy region of the Th^{234} 63- and 93-keV γ rays. Not only is this contribution large but it varies with time as the location of the activity moves along the G.I. tract. To reduce this "noise" tin and copper shielding are used. Some of this is in the ceiling as discussed in the section on the whole-body counter. The remaining Sn and Cu shielding is kept to a minimum by covering the top surfaces of th Pb shield with a layer of 1/16-in. Sn and then with 10-mil Cu and by usi an easily removable curved masonite form (radius = 21 in.) covered with 1/16-in. Sn and 10 mil Cu, with the Cu nearest the subject.

(2) Measurement of Ra^{224} and Th^{234} in urine and feces.

Twenty-four hour collections of urine and feces are analyzed for Ra^{224} and/or Th^{234} by γ counting. Depending on the activity, the sample contained in sealed 2-liter polyethylene bottles, are counted either in the whole-body counter using the 8 in. × 4 in. NaI(Tl) crystal and multichannel analyzer or in a smaller, equally well shielded cave using a 4 in. × 4 in. NaI(Tl) crystal and multichannel analyzer.

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with tap water. Two pairs of standards are made, one pair containing 10 times greater activity than the other.

Th^{234} excretion standards are prepared in the same manner. They contain 30 ml concentrated HNO_3 and 50 ml citrate buffer to keep the Th^{234} in solution and are made to 2 liters volume.

In the ingestion portion of the experiment, the fecal excretion samples and standards are made to a volume of 1 liter to minimize possible leakage at the cover joint, since fecal samples from this experiment contain large amounts of Ra^{224} and particularly Th^{234}.

Activities in the Ra^{224} excretion samples in the injection phase of the study are determined by comparing the sample counting rate in the photopeak of the 239-keV γ ray of Pb^{212} and/or the 2.61-MeV γ ray of Tl^{208}, with that given by a suitable level standard.

In the ingestion phase of the study the excretion samples contain both Ra^{224} and Th^{234}. The Ra^{224} excretion standards are measured to determine the counting rate in the 1.0 MeV region as a fraction of the counting rate in the 2.61-MeV photopeak. This procedure allows a Ra^{224} spectrum to be stripped from the complex spectrum of an excretion sample, thereby permitting a calculation of both Th^{234} and Ra^{224} activities. In those samples where the Th^{234} content is very low (this is especially the case for all the urine samples), the Ra^{224} is allowed to decay after its activity in a sample is determined, and a measure of Th^{234} activity is made several weeks later using the 64- and 93-keV γ photopeak counting rate.

(3) Measurement of Ra^{224} and Th^{234} in blood specimens.

In the injection phase of this study, several 10-ml blood samples are drawn on the day of injection, and one 10-ml sample is taken on each succeeding day for ~5 days. Plastic disposable syringes (12 cc) with the inner surfaces wetted with heparin are used to draw the samples. Of each 10-ml sample taken, 6 ml are transferred from the syringe to a dram flip-top polyethylene vial for β-counting in a well-type, thin-walled, plastic scintillator.* The counting efficiency for 6 ml Ra^{224} and Th^{234} blood samples is ~7%.

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*Manufactured by Baird-Atomic, Inc. The inner and outer cylindrical reflecting surfaces are separated ~0.5 cm from each cylindrical face of [illegible] for maximum light collection.

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For more sensitive measurements of Th^{234} blood samples, 6-ml aliquots are placed in 50-ml porcelain crucibles. No added carrier is needed since the red cells provide adequate Fe carrier. The samples are dried on a hot plate with infrared lamps and then are flamed (this process being short compared with vacuum drying). The ashed contents of the crucibles are washed with 0.1M HNO_3 into stainless steel planchets and are counted in a proportional flow counter, (window thickness = 0.5 mg/cm^2).* The counting efficiency with this device is ~30% with a background of ~2 cpm.

Radium^{224} blood samples are counted with the wall crystal to determine the Pb^{212} activity. For greater sensitivity in the measurement of Ra^{224} in blood samples, use is made of a Tn deemanation method.** Six-milliliter blood samples are placed in 50-ml porcelain crucibles containing 10 mg Ba carrier. The samples are dried as above and muffled overnight at [illegible]°C. The ashed samples are dissolved in 6M HCl, transferred to deemanation tubes,*** and the solutions made to volume (50 ml) with additional 6M HCl. The solution is then deemanated by bubbling water-pumped nitrogen through the tube at a rate of 1 liter per min. Thoron daughters are collected on a copper planchet (1 in. dia.) coated with silver-activated ZnS phosphor, with 3000 v applied, as the Tn-bearing nitrogen passes through a 4-liter collection can. After a suitable collection time (1 hour to several hours), the planchet is counted in an α scintillation counter consisting of activated ZnS phosphor on a phototube face. The activity is sandwiched between this scintillation layer and that on the planchet for ~4π geometry. The over-all efficiency of deemanation and counting is ~30% with a background of 2-4 cph.

In the oral phase of the study, ~30-ml blood samples are taken and processed, as above, for counting of the Th^{234} in the proportional flow counter. The counting is not done until several weeks later to insure that any Ra^{224} in the sample has decayed. Ra^{224} was not measured in these blood samples. A pilot study, in which a subject was administered a dial[illegible]int capsule containing only Ra^{224}, indicated that parameters such as breath Tn and urinary Ra^{224} excretion would serve as satisfactory [illegible]

*Backman Widebeta radiation counter.

**Attempts to deemanate whole blood with the use of various antifoaming agents were not successful because of excess foaming occurring with the [illegible]

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corroborating indicators of uptake and thus minimize additional blood work and sampling from the subjects.

Control blood samples for the injection phase of the study are obtained from laboratory personnel. In the oral phase, two control blood samples are obtained from each subject prior to administration of the radionuclides. Ra^{224} and Th^{234} blood standards are prepared by adding aliquots of standardized solutions to control blood and treating these blood samples by the appropriate methods.

(4) Measurement of Thoron in the breath.

Breath samples are obtained from the Ra^{224} injection subjects and from all of the subjects who ingested simulated dial paint containing both Ra^{224} and Th^{234}. The method of sampling the breath and measuring the Tn content of the sample is a standard procedure in this laboratory. Several samples of the subject's breath are taken on the day of administration, followed by one sample per day for as long as possible.

The subject, wearing a face mask with two 1-way valves, breathes aged air from a balloon reservoir supplied from a pressurized tank. The expired air passes through an ~35-liter chamber containing a copper planchet thinly coated with ZnS phosphor (with a 6000-v potential applied) on which Tn daughters are collected. Care is taken to detect leaks around the face mask by comparing the flow rate from the tank of aged air with the flow rate entering a spirometer. When no leakage is indicated, the collector voltage is then applied. After a sufficient collection period (5-60 min.), the planchet is removed and counted in the α scintillation counter described for the Ra^{224} blood samples. The efficiency of the over-all collection and counting system is ~30%.

A series of sample replications on two of the subjects over short time intervals (<1 hour) indicates that measurements have an error of ±10% when the collection time is 5 or 10 min. though counting errors may be only ±1%. These large variations are due to physiological fluctuations and are reduced with longer collection times. However, counting errors increase as less Tn is released in the breath and the over-all measurement error is essentially constant at ~±10% up to the ~20th day of sampling.

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d. Selection and handling of subjects for study.

The subjects in this study were used for either intravenous calibration experiments or for gastrointestinal studies. No individual participated in both types of study. Healthy male and female volunteer subjects were used, ranging in age from 63 to 83 years. All subjects underwent a complete history and physical examination. They were required to be free of any renal or gastrointestinal disease. Endocrine or metabolic diseases disqualified a subject. Also, any serious recent illness, diseases involving the skeletal system (excepting mild osteoarthritis) or unusual dietary or bowel habits disqualified a subject.

Clinical laboratory studies included a white blood count, hemoglobin, hematocrit, differential blood count, alkaline phosphatase, blood sugar, blood urea nitrogen, serum electrophoresis, urinalysis, serum calcium, and phosphate. All subjects had x-rays of the long bones and skull for the purpose of excluding those with bony abnormalities.

The subjects selected were all in amazingly good health as determined by these usual clinical methods. Table 36 summarizes some of the characteristics and the dose schedules for each subject.

Before the actual experimental study, each subject was interviewed for the purpose of obtaining a background whole-body count and to explain in detail the nature of the entire experiment and the part to be played by each.

During the experimental period, the subjects were housed either in the M.I.T. Infirmary or at the Sancta Maria Hospital adjacent to MIT.* Appropriate measures for collecting urine and feces separately were employed, with a trained nurse in attendance to assure that no inadvertant contamination occurred. Radiological monitoring procedures were employed.

A bedside commode was used for collecting feces in a plastic bag which was then placed in a 2-liter plastic bottle. Urine was voided directly into wide-mouthed plastic bottles. Water was added to all excreta to make up to 1 liter and 2 liters as required, and 10 ml. of concentrated HNO_3 were then added. The bottle covers were sealed with plasticene and tape to prevent leakage.

Excretion samples were further wrapped and sealed in thin polyethylene sheets to prevent any possible contamination. Each stool was individually

*M.I.T. now has a Clinical Research Center, but this facility was not completed in time for this study.

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Table 36. The activity administered to each of the subjects as indicated has an error of ~±5% in the absolute value as determined from standardization measurements. Each subject was thoroughly screened by a medical history and clinical examination as described in the text. Only the pertinent results are indicated in the table to show that the subjects were normal for their age and that the few x-ray findings would probably not significantly affect the outcome of the experiment.

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Table 36. Dose Schedule and Physical Characteristics of Human Subjects

Subject	Dose of Radionuclide Administered		Age	Ht. (cm)	Wt. (kg)	No. of teeth**	Hct (%)	WBC	BUN (mg%)	Ca (mg%)	X-ray Findings
	Ra^{224}* (μCi)	Th^{234} (μCi)									
RIVM1	0.24	--	82	165	58.9	27	44	9700	17	10.5	Degen.changes,rt.knee secondary to trauma.
RIVM2	0.93	--	71	156	65.8	0	47	7400	12	10.3	WNL***
RIVM3	0.89	--	76	160	67.2	0	44	9000	14	9.2	WNL
RIVM5	0.95	--	63	168	72.6	30	46.5	7700	17	9.6	WNL
RIVF1	0.92	--	71	155	66.6	16	41	8300	12	10.0	Slight degen.change of rt. hip.
RIVF2	0.91	--	75	162	80.4	0	40.5	9600	18	10.5	WNL
TIVM1	--	1.20	79	169	63.3	0	46	11000	18	10.8	WNL
TIVM2	--	2.52	72	182	93.1	28	42	9000	20	10.3	Degen. changes L4-5
TIVM3	--	2.57	70	176	64.9	30	40.5	8600	18	9.6	WNL
TIVM5	--	2.80	81	180	78.1	8	47	7300	14	10.4	WNL
TIVF2	--	3.10	79	164	69.0	0	36.5	8400	24	10.9	WNL
TIVF3	--	3.01	72	149	56.8	0	43	10000	14	11.0	WNL
RPOM1	2.45	--	72	175	85.6	11	48	9200	18	10.3	Osteochondroma,lt. upper femur.
TPOM1	--	120	77	170	86.0	0	46	5700	20	10.8	Aging changes in arms and forelegs.
TRPOM1	1.24	89.6	83	168	65.4	0	43.5	8900	16	9.1	Aging changes in both radii, WNL.
TRPOM2	3.88	141	63	175	79.9	0	43.5	9200	14	10.2	WNL
TRPOM3	3.13	123	75	159	68.8	0	44	7700	15	9.9	WNL
TRPOF1	0.135	247	72	163	76.5	8	42	9100	15	9.4	WNL
TRPOF2	0.132	173	81	146	58.3	24	46	6000	16	9.5	WNL
TRPOF4	0.107	203	77	149	51.3	26	41	9100	13	10.8	Degen. changes about symphysis.

*Ra^{224} activity only; γ-emitting daughters are ~1.15 times these activities at equilibrium.

**The SXB results show no correlation with number of teeth, but this information is presented for the record.

***WNL = Within normal limits.

Subject Code:

RIV = Ra^{224} intravenous
TIV = Th^{234} intravenous
RPO = Ra^{224} oral
TPO = Th^{234} oral
TRPO = Ra^{224} + Th^{234} oral
M = Male
F = Female

collected and measured. Urine was composited on a 24-hour basis before measuring.

Intravenous administration of the isotopes was done in the M.I.T. Infirmary. Oral administration was carried out in the laboratory. No difficulties were encountered in either route of administration.

All blood specimens were obtained by intravenous puncture, using the arm opposite to that where the isotope had been injected, for those subjects receiving the isotope intravenously. Heparin was used as the anticoagulant and disposable plastic syringes and needles were used throughout.

Before the start of the intravenous and oral experiments, each subject in the group was measured in the chair, arc, and H3SXB, and L8SXB positions for control values. Control samples of blood, urine, and feces were taken as needed before the administration of the activities.

e. Radioisotope administration.

(1) Method of intravenous administration.

Intravenous injections* are carried out after first measuring the activity of the contents of the syringe. After administering the radioactive solution to the subject a second measurement is made of the activity of the residual contents. The activity administered is the difference in these two measurements, obtained without a knowledge of the exact volume injected or the exact specific activity of the solution.

Several days before the experiment starts disposable syringes (2.5 ml) are filled with the radioactive solution to the appropriate volume (~1 ml) and the hub tip is rescaled with the sterile plastic tip. The plastic tip is secured with tape and the plunger is fixed to prevent accidental discharge or release of the solution. The sealed syringes are sealed in small polyethylene bags and stored in a refrigerator. Several measurements are made in the intervening period to determine that the parent activity and daughters are in equilibrium. After injection in either the left or right antecubital vein, the system is rescaled, including the needle used, and again remeasured several times. All measurements are made by γ counting using appropriate standards.

Syringes containing Ra^{224} are standardized against an aged $Th(NO_3)_4$ standard as described in Sec. b. Prior to injection, Ra^{224} and its

*All injections were carried out by Dr. Martin Lubin of the M.I.T. Medical

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daughters are in transient equilibrium. Several γ measurements on each syringe after injection indicate that the amounts of Ra^{224} and its daughter Pb^{212} remaining in the syringes immediately after injection are not in their pre-injection ratios. The ratio of Pb^{212} to Ra^{224} injected is ~95 percent of the equilibrium ratio in each case, and a correction is applied to the early counting data on the subjects in order to account for this non-equilibrium.

Post-injection measurements on the syringes did not commence sufficiently soon to allow a determination of the amount of Bi^{212} ($T_{1/2}$ = 60 minutes) which remains in the syringes. However, measurements of early blood samples show a growth of activity consistent with the half-period of Bi^{212}, thus indicating either a rapid clearance of Bi from the blood, or a considerably less than equilibrium amount of Bi injected. The latter possibility is supported by the work of F. Scholes[37] whose experimental methods and results on Ra^{224} injected in man closely parallel those of this study.

Syringes containing Th^{234} are standardized against a 1 g standard of pure U_3O_8 in 4 ml HNO_3, as described in Sec. b. Prior to injection, Th^{234} and its protactinium daughters are in transient equilibrium. Measurements on the syringes a few hours after injection indicate that Th^{234} and its protactinium daughters are injected essentially in equilibrium.

(2) Method of oral administration.

Oral administration of the Ra^{224} and Th^{234} contained in the capsule is, in principle, simple. The outer protective capsule is removed, the capsule with the activity is transferred to a plastic spoon, the subject wets his mouth with water, then places the capsule in his mouth and swallows it with 25-50 ml H_2O. The difficulty in the administration arises from the small weight of the capsule contents. The capsule is so buoyant that it tends to stick to the roof of the mouth or become lodged in the esophagus.* These

37. F. Scholes, "The Excretion of Thorium X and Its Daughter Products after Intravenous Injection in Man", chap. in Assessment of Radioactivity in Man, Vienna, 1964.

* Preliminary experiments were conducted with capsules containing $BaSO_4$ to determine whether a double encapsulated pill (a safety measure to prevent contamination of the mouth and esophagus) required too long a time for dissolution of the gelatin in the stomach. X-ray examination showed that 40-60 min. were required. This was deemed too long and a single capsule was used, requiring ~20 min. for dissolution. In one of these experiments, the capsule could not be found in the expected regions and was eventually located ~2/4 of the way down

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problems can be minimized by moistening the capsule well while it is in the mouth, taking care to prevent crushing the capsule. After swallowing the capsule, the subject continues to take several small drinks (15-25 ml) to ensure that the capsule enters the stomach. Actual entry into the stomach region is confirmed by measurements with a survey meter over the chest and upper abdominal areas.

The gelatin capsules containing both Ra^{224} and Th^{234} in a simulated dial paint are standardized simultaneously for both nuclides. A capsule containing only Ra^{224} in simulated dial paint is first measured to determine the counting rate contribution to the 1.0-MeV Pa^{234m} γ photopeak region in the Ra^{224} spectrum as a fraction of the counting rate in the photopeak of the 2.61-MeV γ of Tl^{208}. Thus, the Ra^{224} spectrum can be stripped from the complex spectrum of the capsules containing both Ra^{224} and Th^{234}. Serial measurements confirm that both Ra^{224} and its daughters and Th^{234} and its protactinium daughters are in transient equilibrium prior to ingestion. The outer gelatin capsule, used to protect the smaller capsule until administration, and the spoons used to administer the capsules, are γ-counted after administration and are found to contain no activity.

5. Presentation and Discussion of Results

This section contains the data and results of the experiment divided into two major parts: (1) the intravenous studies including the calibration data required for the second part and the metabolism data representing a bonus derived from the calibration requirements, and (2) the oral studies providing the answer for which the whole experiment was designed.* The

*All the procedures were tested on dogs prior to conducting the experiment on human subjects. The results of these preliminary experiments are reported in progress report form[38,39] and are consistent with the results obtained on dogs at the University of Utah[40,13]. From the experimental point of view, our experiments indicated the difficulty of interpreting the results on the Th^{234} measurements using its 64- and 93-keV γ rays in the first few days after the oral administration. Furthermore the results showed that the uptake of Ra^{224} might approach ~10 times the anticipated few percent in human beings. The adequacy of the SXB measurement technique was also demonstrated by comparing the body burdens with the known body burdens obtained by difference between the amount excreted and that administered.

38. C.J. Maletskos, et al., "Differential Uptake of Elements 88 and 90 Following Oral Ingestion by Human Beings", NYO-9505, pp. 59-79 (May 1963).

39. C.J. Maletskos, et al., "Differential Uptake of Elements 88 and 90 Following Oral Ingestion by Human Beings", M.I.T.-952-1, pp. 113-149 (May 1964).

40. B.J. Stover, D.R. Atherton, and C.W. Mays, "Studies of Retention and Distribution of Ra^{226}, Pu^{239}, Ra^{228} (MsTh1), Th^{228} (RdTh) and Sr^{90} in Adult Beagles", in Some Aspects of Internal Radiation,

Ra metabolism results constitute an addition to the meager information on the metabolism of Ra in human beings, especially at short times after intravenous administration. The results on the intravenous injection of Th are the first of their kind in human subjects to the best of our knowledge.

All data are corrected for the physical decay of Ra^{224} and Th^{234}.

a. Results and discussion on Ra^{224} injected intravenously.

The principal physical characteristics of the human subjects used in this study and the amounts of radionuclides administered are given in Table 36.

The primary Ra^{224} body γ measurements are shown in Figs. 76a-e, consisting of results using the chair, arc, and low- and high-energy SXB positions. The order of decreasing sensitivity for those positions is LSXB, chair, HSXB, and arc. The resulting curves for each individual are essentially parallel leading to average ratios between the positions as follows: LSXB/chair = ~3; LSXB/HSXB = ~4; chair/arc = ~10.

There appears to be a difference in the first few days between the SXB measurements and the chair and arc measurements, with the ratios SXB to chair or to arc being less than those occurring later. This difference is explainable on the basis that the Tl^{208}, or more likely the Pb^{212}, or perhaps even the Ra, has a distribution varying with time. Indications that this is so are given by the study of Schales[37] in which a subject given an intravenous injection of Ra^{224} (for ankylosing spondylitis) was scanned over the length of the body. The curve peaks at about the mid-abdominal region; by the eighth day this distribution has changed to one in which the activity essentially decreases from head to toe and presumably persists for a while. In the chair and arc position, the increased activity over the upper abdomen will be reflected in the measurements, while the measurements in the SXB positions will not detect this activity. The variation in this ratio terminates shortly after 5 days consistent with the observation of Schales.

The calibration factors (net cpm/μCi retained) for the chair and HSXB position are shown in Figs.77 and 78. The microcuries retained are calculated from excretion data and are consistent with the arc measurements. The data show more variability than would be expected from repositioning and counting errors, and probably represent some effects of [illegible]

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and of the variable Ra^{224} content in the bowel which can be signifi the first few days. The data show some trends and the values at t ≥4 days are presumably the more reliable and representative of l times. The adequacy of the chair calibration value can be determi comparison with the chair calibration value obtained for subjects w skeletal burdens of Ra^{226} and Ra^{228} of 30-40 years duration. The a value of 1530 ± 12% ($\bar{x} \pm \sigma_{\bar{x}}$) cpm/μCi retained* is not significantly different from 1500 ± 5% cpm/μCi retained found in 5 human subjects (4 females and 1 male) with long-term body burdens of Ra^{226} and Ra^{2} determined on an absolute basis by the arc method[41]. For purposes calculating retention beyond t = 4 days, the calibration factor of individual at t = 4 days is used. The results on the H3SXB calibra presumably reflect changes and variations similar to the chair calib and are expected to be just as reliable. The average value at t ≥ 1010 ± 16% cpm/μCi retained, includes all subjects and is the value used for determining the absorption of Ra^{224} in the oral part of th periment. The large value of the standard deviation of the mean (1 reflects the low value for one subject (RIVF2) (the calibration fac is 1160 ± 9% without this woman), but is satisfactory for the needs the absorption measurements.

The urinary and fecal excretion results are given in Table 37. excretion data provide the information needed though not as reliabl might be obtained from a longer observation period. The daily urin excretion is proportional to the blood activity within the accuracy sets of data (see Figs. 81a-c). The daily fecal excretions are as is usually the case. The proportionality of the fecal activity the blood activity cannot be substantiated from these data, although is known to be so from many other experiments in other animals and chemical analogues such as Ca and Sr. The most reliable feces-to-ur

*The value of 1530 ± 12% is obtained from the average value of 17 as given in Fig. 74, divided by 1.15. The value of ~1.15 is th tivity ratio between Bi^{212} and Ra^{224} when in transient equilibri situation assumed to exist for Ra^{224} several days after administ In the case of long-term Ra^{220} burdens, the factor does not appl since secular equilibrium is assumed for this condition.

41. R.D. Evans, R.A. Dudley, C.J. Maletskos, M.I.T. Radioactivity Ca Progress Report, pp. 1,2 (May 1951).

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Table 37. The complete excretion results are summarized in this table which indicate that >50% of the Ra^{224} is excreted in 5 days and that the feces-to-urine ratio averages ~30 ± 6. Values in parentheses are predicted from the arc measurements on the subject. The directly measured fecal excretion is lower than indicated by the arc measurements on the residual activity in the body. In view of the expected reliability of fecal collection, the reason for the discrepancy is not known. There is evidence, however, to suspect that one fecal sample from subject RIV:5 was not collected but no proof has been found. The feces-to-urine ratio stabilizes in ~2 days, starting out with lower values.

Table 37. Excretion of Ra^{224} by Human Beings Following Intravenous Administration

Subject (uCi injected)	Time after injection (days)	Daily urine %	Daily feces %	Cum. urine %	Cum. feces %	Cum. total %	Cum. feces / Cum. urine
RIVM2	1	0.95	12.5	0.95	12.5	13.5	13.2
	2	0.27	10.9	1.22	23.4	24.6	19.2
	3	0.19	28.6	1.41	52.0	53.4	36.8
	4	0.07	4.95	1.48	57.0	58.5	38.5
	5	0.09	10.9	1.58	67.9	69.5	42.9
RIVM3	1	3.38	3.17	3.38	3.17	6.55	0.94
	2	0.35	32.8	3.73	36.0	39.7	9.65
	3	0.15	10.7 } (29.7)	3.88	46.7	50.6	12.0
	4	0.06	1.48	3.94	48.1 (65.7)	52.0 (69.6)	12.2 (16.7)
	5	0.05	0.89	3.99	49.0 (66.6)	53.0 (70.6)	12.3 (17.7)
RIVM5	1	2.16	0.73	2.16	0.73	2.89	0.34
	2	1.26	0.18	3.42	0.91	4.33	0.27
	3	0.11	1.10	3.53	2.01	5.54	0.57
	4	0.07	----- (38.0)	3.60	2.01 (40.0)	5.61 (43.6)	0.56 (11.1)
	5	0.10	2.02	3.70	4.03 (42.0)	7.73 (45.7)	1.09 (11.3)
RIVF1	1	1.00	-----	1.00	-----	1.00	-----
	2	0.36	42.1	1.36	42.1	43.4	30.9
	3	0.19	-----	1.55	42.1	43.6	27.2
	4	0.15	-----	1.70	42.1	43.7	24.8
	5	0.10	13.8	1.80	55.9	57.7	31.0
RIVF2	1	0.66	-----	0.66	-----	0.66	-----
	2	0.17	13.9	0.83	13.9	14.7	16.8
	3	0.10	17.1	0.92	31.0	31.9	33.7
	4	0.07	10.8	0.99	41.8	42.8	42.2
	5	0.05	3.7	1.04	45.5	46.5	43.7

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ratios are obtained from the cumulative data with the best values occurring at t = 5 days. The average value of F/U = ~30 and most frequently the value is 5~10; almost all the Ra is excreted via the feces.

On an absolute basis, the urinary Ra excretion is equivalent to the clearance of ~230 mg Ca/day. This value is comparable to the normal adult daily calcium excretion of ~200 mg Ca/day. On the other hand, the Ra fecal excretion is 30 times greater and would correspond to an endogenous calcium excretion of ~7000 mg Ca/day. This value is much larger than the normal endogenous fecal excretion, ~200 mg Ca/day. As summarized by Mays[42], the retention of the alkaline earths by many species is essentially the same. The big exception is the retention of Ra in man. The retention is much lower and this is most likely due to the large loss of Ra through endogenous fecal excretion. The F/U ratio of ~30, is comparable with the value of 35 in one subject of Schales[37], with 140 in one subject of Mays[43], with ~21 of Soil et al.[11], twice in one subject), with 55 of Morris et al.[12], and with 75 of Lucas et al.[44], the last two in subjects with long-term Ra^{226} burdens.

The Ra^{224} retention is shown in Figs. 79 and 80. The semilog plot of Fig. 79 shows a rapid decrease in retention to ~17 percent in 20 days. Generally, the shape of the average retention curve has the form of two exponential components, ~70% of the dose with a $T_{1/2}$ = ~2 days and ~30% of the dose with a $T_{1/2}$ = ~20 days. These data are not adequate for rigorous mathematical treatment and were obtained to give some indication of the Ra retention in human beings shortly after administration and to see how well the power function of Morris et al.[12] fits the data in the early post-injection period. Whatever the implications of the dynamics of Ra metabolism by either the exponential or power function equations, the latter is the most useful method for making radiation dose calculations for Ra in man. The results of the power function plots in Fig. 80 indicate that all the experimental results are above the

42. C.W. Mays, W.R. Christensen, R.D. Lloyd, D.R. Atherton, W.W. Parsley, and G.S. Pitchford, "Radium Studies in Man Soon after Injection", Research in Radiobiology, Univ. of Utah, COO-226, pp. 71-77 (Sept. 1952).

43. C.W. Mays, R.D. Lloyd, W.R. Christensen, D.R. Atherton, and G.S. Pitchford, "Radium Metabolism in Man", Research in Radiobiology, Univ. of Utah, COO-227, p. 224 (March 1953).

44. H.F. Lucas, J.H. Marshall, and L.A. Barrer, "The Level of Radium in Human Blood Forty Years after Ingestion", ANL-6760, pp.75-78 (June 1963).

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Fig. 79. Retention of Intravenously Administered Ra^{224}.

The retention results shown are compiled from two sets of measurements, those indicated by the solid lines and those indicated by the dotted lines. The former represent results based on excretion and the latter represent results from chair measurements. This semilog plot indicates a somewhat rapidly decreasing component in the retention soon after administration. There does not seem to be any particular difference between the sexes. The bold solid line represents the average retention of all the subjects.

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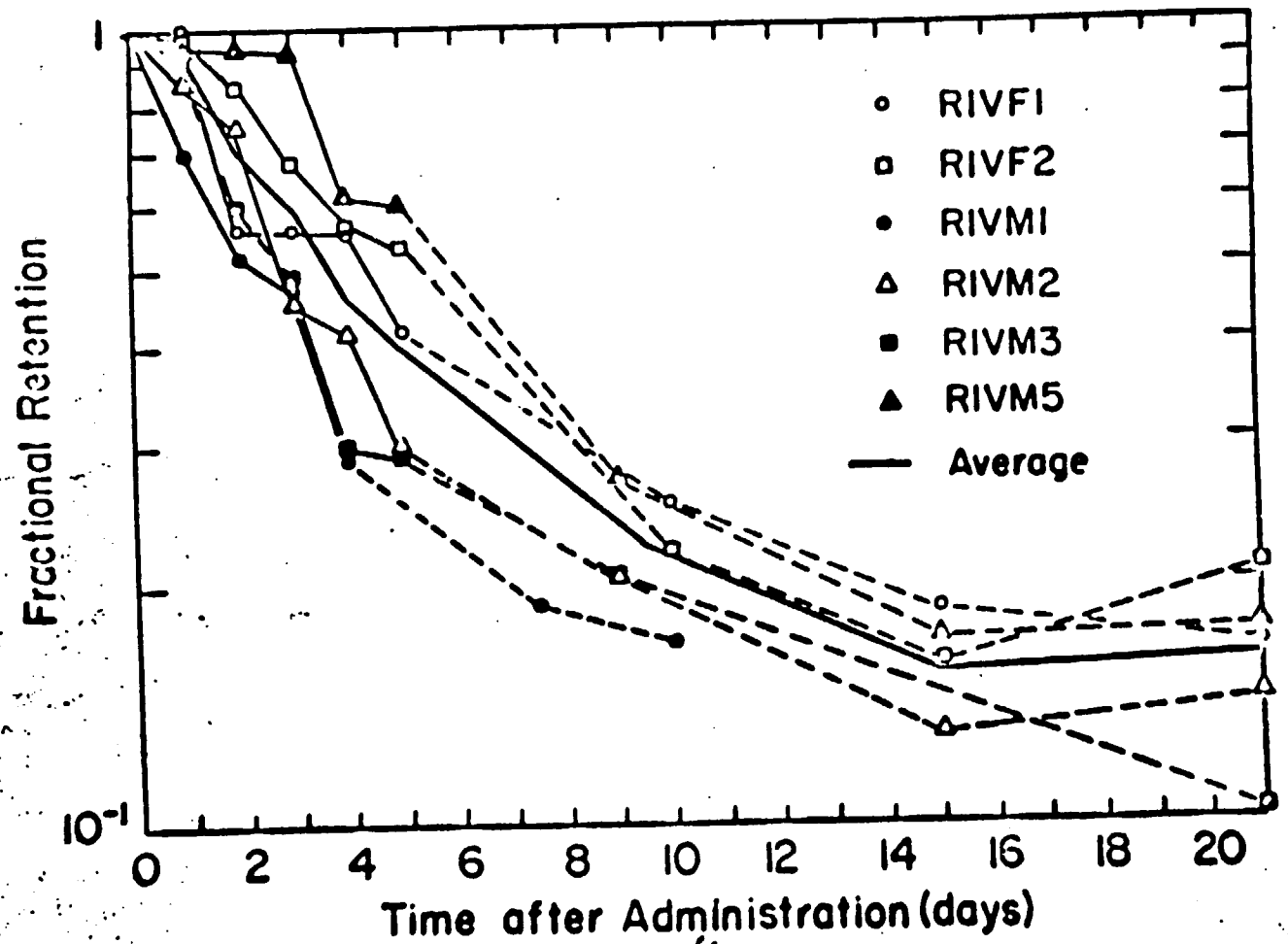
RIVF1
RIVF2
RIVM1
RIVM2
RIVM3
RIVM5
Average
Fractional Retention
1
10^{-1}
0
2
4
6
8
10
12
14
16
18
20
Time after Administration (days)

Fig. 79.

Fig. 80. Retention of Intravenously Administered Ra^{224}.

The retention results are plotted in log log form for comparison with the results obtained by Norris et al. which are shown as a power function curve. The observed retention up to 20 days is higher for the subjects than the average value of Norris. This effect may be due to the fact that there are still significant quantities of Ra^{224} in non-bony tissues and also because of the age of the subjects with less Ra incorporated in the skeletal tissues. The average value of these 5 subjects appears to converge to the equation of Norris et al.[12]

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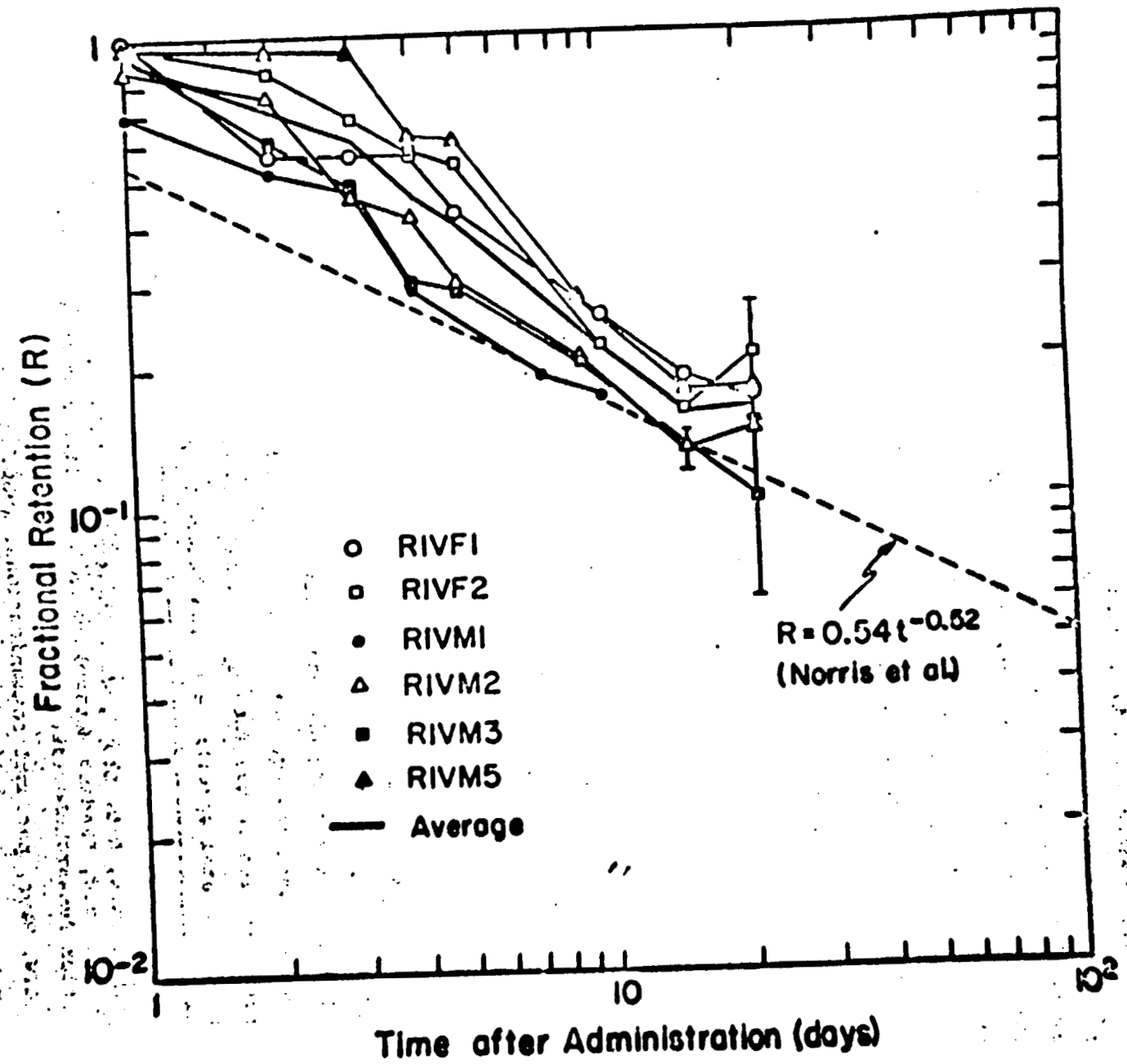

Fig. 80

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The behavior of Tn in the exhaled breath is indicated in Fig. 82, showing that fraction of all the Tn produced in the body which gets outside (losses into the G.I. tract and by sweating are negligible). With the short half-period of 54 sec., the amount of Tn which is exhaled from the body 5-10 min. after administration of the Ra^{224} is remarkably high at 10% of the dose. The Tn drops rapidly with time approaching ~0.2% dose at t = ~20 days. The shape of this curve is not the shape of the blood curve since Tn in the blood is supported by Ra^{224} in the blood, in soft tissue, and in the skeleton. At t = ~20 days the Ra^{224} concentration is ~2×10^{-3}% dose/l serum. The breath Tn concentration can be calculated from the expression (p. 308 of Aub et al.[4]) $\gamma = \lambda_{Tn}(bX)/Z$ μCi/l where γ_{Tn} is the decay constant of Tn, (bX) is the Tn external to the body, which contains the quantity X of Ra^{224}, and Z is the breathing rate in l/min. The breath Tn concentration is γ = ~0.06 (bX) for a breathing rate of 12 l/min., the average of all subjects. At t = ~20 days, γ = ~(0.06/l) (~0.2% dose) = ~0.01% dose/l when the serum contration is ~0.002% dose/l. Thus, the concentration ratio between breath and serum is ~5. The Ra^{224} retention in the body at t = ~20 days is, however, ~20% dose and, if all the Tn could get to the blood, would lead to a serum Tn concentration of 20% dose/3 l serum = ~7% dose/l serum. This value is ~700 times the breath concentration and indicates that most of the retained Tn and, in turn, the Ra^{224} is incorporated fairly well in the skeletal tissue, even accounting for Tn loss during its transit time in the circulating blood. The degree to which this has occurred is shown in Fig. 83 in which the Tn outside the body is shown as a fraction of the retained Ra^{224}. In ~4 days the exhaled Tn drops to ~1-2% of the retained Ra^{224} and remains essentially constant over the remaining period. This result leads to the conclusion that the Ra^{224} does not redistribute much beyond t = ~4 days and supports confidence in the calibration factors for the chair and HOSXB positions. The decrease in the external Tn is very slow beyond the 4th day. Eventually the decrease extends an order of magnitude lower, to 0.1% of the retained dose, some 30-40 years later, based on the long-term retention of Ra^{228} in man[50].

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50. R.A. Dudley, "Calibration of Fraction of Tn Exhaled in Ra-MsTh and in Thorotrast Cases", M.I.T. Radioactivity Center, Progress Report, pp. 2-5 (May 1950).

An alternative way to look at the Tn results is to consider that Tn is retained in bone, because of its short half-period, just as well as R is at times long after administration in Ra toxicity cases. This Rn retention is ~1/3, presumably dependent on the ratio of mineral density to total density [Mays et al.[51]] , while the remaining ~2/3 has an opportunity to get in the blood stream and be exhaled. In the case of Tn, ~2% of the total or ~3% of this exhalable 2/3 gets out, leading to an effective travel time of ~4.5 min. This travel time eventually increases to ~8.4 min. many years after when the external Tn is ~0.1% of the retained Ra^{224}. Since this travel time of ~5 min. is long compared with circulation times, the increase to ~8 min. over the years would indicate progressive burying of Ra^{224} into bone and hence increased difficulty for the diffusion of Tn from bone to the blood stream.

The relationship of the whole-body specific activity to that of the blood is shown in Fig. 84. It is admittedly somewhat premature for this type of correlation but it represents an attempt to see when the cross-over point occurs as an additional piece of information in the metabolism of Ra by man.

The experimental blood specific activities from the data of Mays[42,4] and from this experiment are not inconsistent with the blood specific activity curve calculated as described in the caption of Fig. 84. The blood data from Lucas[44,52] et al., obtained on 4 subjects at ~45 years after administration of Ra^{226}, are positioned in the graph by their ratio to the body specific activities obtained at the same time (average ratio = $\sim 10^{-2}$). These blood data cannot be positioned on an absolute basis since the fractional Ra^{226} retention for these subjects is unknown. Measurements on Ra^{226} excretion for the 4 subjects, made by Lucas et al. give an average excretion coefficient ($\sim 8 \times 10^{-5}$ per day) which is consistent with that predicted by Marshall's theory at $t \geq t_y$ (t_y = equilibration time). The assumption that the body retention of these 4 subjects

51. C.W. Mays, M.A. Van Dilla, R.L. Floyd, and J.S. Arnold, "Radon Retention in Radium-injected Beagles", Radiation Res. 8, 480-489 (1958).

52. R.E. Rowland, personal communication (Jan. 1965).

Fig. 84. Comparison of Blood and Skeletal Ra^{224} Specific Activities.

This figure is a composite of the data from this experiment, the information from Norris et al.[12], Mays et al.[42,45], Lucas et al.[44,52] and Marshall[53]. The blood specific activity is calculated as Ra^{224} % dose/ml divided by g Ca/ml. Whole-body specific activity is calculated as total Ra^{224} retention divided by calculated total Ca, and is used as a measure of skeletal specific activity. The dashed line for whole-body specific activity represents Norris's retention function, $R = 0.54\ t^{-0.52}$. The dashed line for the blood specific activity curve represents the derivative of the Norris retention function and has a slope of $t^{-1.52}$. Its location on the figure is determined by its intercept at t = 1 day, calculated using Marshall's expression for plasma specific activity, which involves the Norris function derivative and the Ra^{224} "plasma" (blood) clearance for the 5 subjects (~7 g Ca/day). The transition from power function to exponential function (dot-dash curves), for both blood and body specific activities takes place at the equilibration time t_y. This time is calculated as 6500 days from Marshall expressions using the Norris function parameters and the experimental plasma clearance value of 7 g Ca/day.

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has been following the power function of Norris et al. and has, at about $t = t_y$ undergone a transition to an exponential function, as proposed by Marshall, allows positioning the Lucas blood data on a basis consistent with the average excretion coefficient determined for the subjects.

The whole-body specific activity data for the 2 subjects studied by Mays straddle the Norris curve: the higher retention is that of an 80-year-old male, while the lower is for a 41-year-old male. In agreement with Mays' older subject, the results from this experiment on elderly subjects are all above the Norris curve. This deviation from the Norris curve by older subjects could be due both to the effects of age and to soft tissue Ra content. On the other hand, none of the subjects reported by Norris et al. were measured at such early times. Also there are indications that the Norris equation may be modified as a result of a continuing evaluation and reevaluation by Miller[54] of the subjects and of the data studied by Norris et al.

The crossover time (t_x), at which the blood and body activities are equal, is ~75 days, with a probable range of 40-150 days. An earlier attempt to determine the crossover time for Ra in man by Rowland[55] resulted in a value of ~7 months. However, early blood data were not available at the time and the ratio of blood specific activity to skeletal specific activity for 30-40 years after administration as calculated by Lucas was too small (inadvertently) by a factor of ~2. Knowledge of the crossover time is important in the study of the dynamics of Ra metabolism and in the interpretation of bone autoradiographs, especially for the evaluation of radiation dose distributions as discussed by Marshall[53]. For comparison with another alkaline earth, the crossover time for Ra is considerably shorter than the value of 360-710 days reported by Marshall[53] for Sr in man.

The information in Fig. 84, then, is the best available, but it is not as adequate as would be desired. It is obvious that much more remains to be done for a more precise knowledge of the dynamics of Ra in man.

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54. C.E. Miller, personal communication, 1966.

55. R.E. Rowland, "Resorption and Bone Physiology", in Bone Biodynamics H.M. Frost, ed., pp. 335-351, Little, Brown, and Co., Inc., 1964.

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An accurate description of retention is necessary in order to evaluate adequately the internal radiation dose received by individuals having Ra^{226} and Ra^{228} burdens for many years. The radiation dose provides a common base for correlating the biological effects observed in such subjects. If it can be shown that the radiation dose cannot be known to, say, within a factor of ~2 with all the information now at hand, then serious consideration should be given to a long-term study of Ra metabolism in human beings. With the present knowledge of Ra metabolism and toxicity, it would appear that a long-term study can be conducted with safety to the individual using ~1 μCi Ra^{226} and sensitive whole-body and sample counting devices.

Since Pb^{212} is a daughter of Ra^{224} and is present at the time of injection and at later times, it is possible to give some information on the metabolism of Pb^{212} by human beings. The results are shown in Fig. 85 which demonstrates the relationships between blood and body Ra^{224}, blood Pb^{212}, and breath Tn.

The Pb^{212} blood activity values increase slightly in the first few hours. This increase, however, cannot be explained as a further growth of Pb^{212} from its parent Ra^{224}. The reasons for this are that the Ra^{224} is being cleared rapidly from the blood and that the considerations of parent-daughter relationship are such that the Pb^{212} cannot increase in absolute amount when it is initially present at 109% of the activity of its parent Ra^{224} (i.e., ~95% of its transient equilibrium value). This increase in the Pb^{212} blood activity is similar to that observed by Stover[56] in dogs injected with pure Pb^{212}.

The peak value of ~2/3 of the administered dose is consistent with Stover's results, and with the Pb^{212} blood results on a dog injected with Ra^{224} and Pb^{212} in preliminary studies for this experiment[38]. Stover's explanation for this increase is based on the combined effects of relatively long-term attachment of Pb^{212} to the red blood cells and the further attachment of Pb^{212} returning from other compartments to which it had cleared from the plasma. This explanation is a reasonable interpretation of the dog data and would appear to be applicable to the results on the human beings.

The decrease with time of the Pb^{212} blood values is slower than that due to physical decay, indicating that Pb^{212} in the blood is being supported by the decay of Tn in the body at a rate faster than the combined

56. Betsy J. Stover, "Pb^{212} (ThB) Tracer Studies in Adult Beagle Dogs", Proc. Soc. Exp. Biol. Med. 100, 269-272 (1959).

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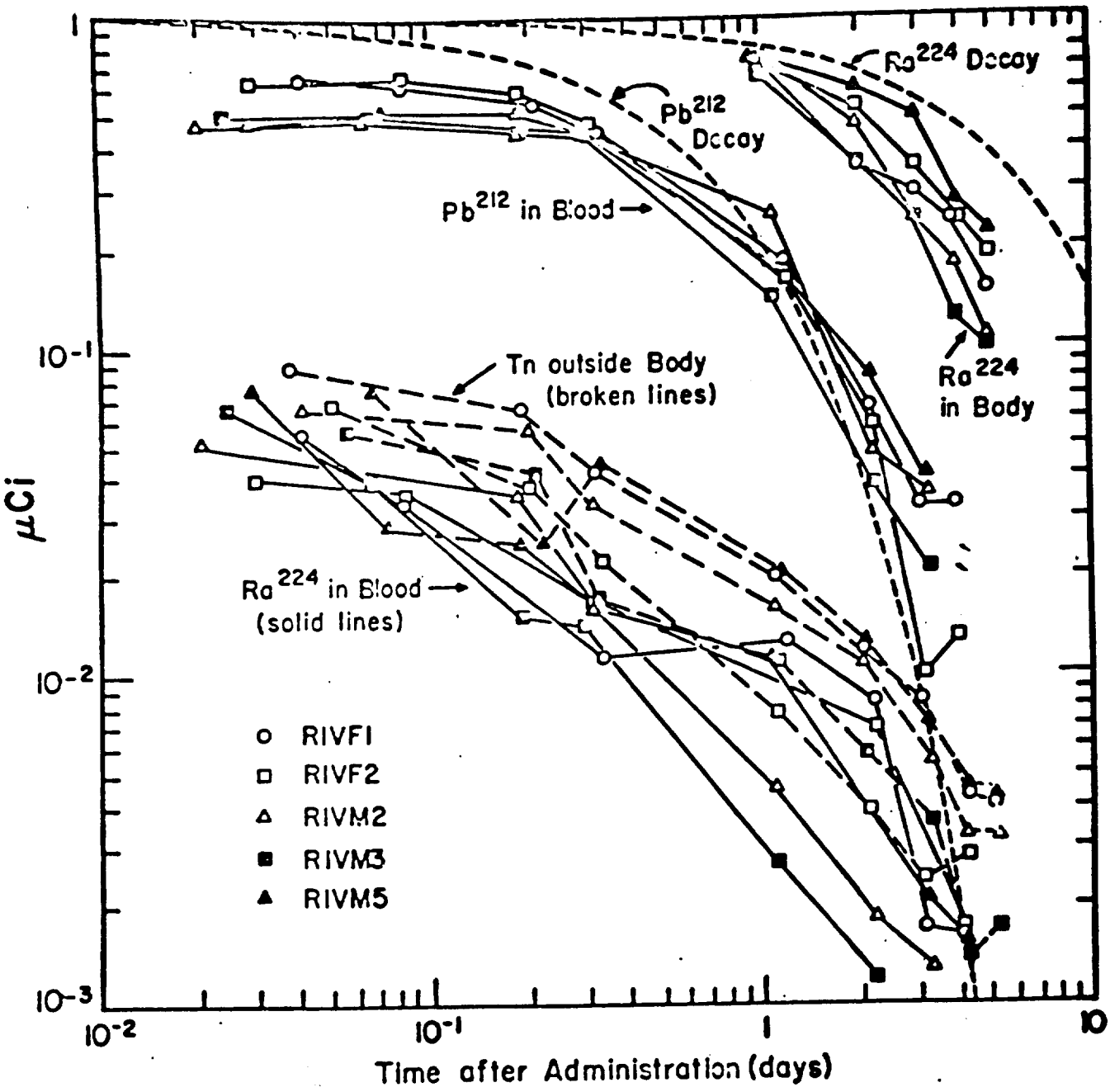
Ra224 Decay
Pb212 Decay
Pb212 in Blood
Tn outside Body (broken lines)
Ra224 in Body
Ra224 in Blood (solid lines)
RIVF1
RIVF2
RIVM2
RIVM3
RIVM5
μCi
1
10-1
10-2
10-3
10-2
10-1
1
10
Time after Administration (days)

Fig. 85.

effects of physical and biological decay. It is not clear from the results of Fig. 85 how much blood Pb^{212} is supported by Th in the blood, much as this relationship would be useful in the study of Ra or Thorotrast toxicity.

The urine and feces excretion samples were not measured soon enough to yield definitive results on the excretion of Pb^{212}. The results indicate that the daily urinary excretion of Pb^{212} is ~1-2 times the daily Ra^{224} urinary excretion indicating that excretion from the kidney can be as high as ~2-4 times that of Ra^{224}. The Pb^{212} activity in the daily fecal samples is ~1/3-1 times the Ra^{224} activity at the end of the 24-hour collection periods, indicating that transfer of Pb^{212} into the G.I. tract is probably ~≤ 1/6-1/2 that of Ra^{224}. From these results it is concluded that ≥90% of the Pb^{212} decays in the body.

Finally, the adequacy of the arc measurements for the independent determination of body burdens is assessed by comparison with the calculated retention obtained from the excretion measurements. Three arc measurements for each subject are compared with the calculated retention during the first 5 days when excretion collections were made. In Table 38 the results indicate no significant difference between the measurements for each subject from t = 1 to t = 4 days, at a time when redistribution of Ra^{224} and/or daughters was taking place. However, in addition to the fact that the accumulated errors increase up to t = 4 days, subjects RIVM3 and RIVM5 have significantly lower values at t = 4 days. As stated in the footnote of Table 37, incomplete fecal collection for subject RIVM5 is suspected, but this is not so for subject RIVM3. Excluding these two values, the conclusion is that the arc method gives valid body burden results within ~±5%. This arc method was developed ~30 years ago by Evans[35] and the comparison just made provides the first test of his procedure for measuring Ra body burdens.

The adequacy of the arc method is substantiated even further by the close assessment of body burden even when the burden is a point source in the G.I. tract. Measurements were made during the pilot runs in which the Ra^{224} activity was administered orally in pill form (to subject RIVM1). The arc measurement was made immediately after ingestion and at t = 1 day. The calculation of body burden was made using an average body attenuation

With ≤15% increase being expected from the disequilibrium of the 6.7-hour Pa^{234} the reason for the remaining increase is not known. Since the ratio of L8SXB/L3SXB has the same value of ~15 for both men and women it can be concluded that Th^{234} and Pa^{234} are present in the same ratio in that portion of the body.

The reason for the difference in distribution between men and women is not known. If there is 50% more activity in the upper part of women, comprising ~20% of the skeleton, then there should be a deficit of ~10-15% shown by the chair measurement. A 10-15% change in the chair measurement is easy to observe and is not found (Fig. 87). This conclusion is further substantiated by the liver shielding experiments, described later, conducted to see whether a significant excess of Th^{234} was present in the liver.

The urinary and fecal excretion results are given in Table 39 and show that the total excretion is low and predominantly in the urine. The daily urinary excretion is proportional to the blood activity (Fig. 91); the fecal data are too variable to arrive at such a conclusion even though this proportionality is expected. The most reliable urine-to-feces ratios are obtained from the cumulative data and the results indicate a U/F ratio of 10 for males and ~20 for females. This is the second instance of a sex difference in the metabolism of Th^{234}. No reason can be given for it at this time and it is not known whether this observation is related to the sex difference found between the SXB and chair measurements.

The retention, calculated both from the excretion and body measurements, is shown in Fig. 90. Most of the decrease takes place in the first 5-10 days, at which time the retention is ~92% and changes very slowly up to ~110 days. The average biological half-period for retention ranges 2 years to ∞ for the observation period of 0.3 years. For all practical purposes, the biological half-period of Th is long enough that it can be neglected in any dosimetric calculations involving Th^{228}.

The results for blood are shown in Fig. 91. Even though the activity drops rapidly, the rate of decrease is considerably slower than that for ^{234}

unusual distribution and lend confidence to the arc results when the activity is distributed more generally throughout the body.

b. Results and discussion on Th^{234} injected intravenously.

The results on the Th^{234} injected intravenously are presented in the same fashion as the results on the Ra^{224} injected intravenously. Because the general form of the presentation has been made, the Th^{234} results can be given more rapidly, focusing attention on unusual features.

The primary Th^{234} body γ measurements are shown in Figs. 86a-e, consisting of results on the chair, arc, low-, and high-energy SXB positions. The order of decreasing sensitivity for these positions is L8SXB, chair, H8SXB, and arc, the same as for Ra^{224}. The precision of the arc measurements is not as great for Th^{234} as it is for Ra^{224}, because of the low abundance of the 0.77- and 1.00-MeV γ rays. The constancy of the values for the L8SXB position is unusual. The chair values show a small downward trend, while the H8SXB results show some variation with a tendency to peaking at t = ~2-3 days. The sensitivity ratios are as follows: L8SXB/H8SXB = ~15; chair/arc = ~10. The observation of an apparent sex difference in the ratio, L8SXB/chair, of ~15 for women and ~10 for men is unexpected. A corresponding sex difference for the ratio, H8SXB/chair, is also noted. This appears to be an intrinsic sex difference for Th and is not related to a disequilibrium between 6.7-hour protactinium and Th^{234} which may cause a difference of at most ~15%.

The calibration factors (net cpc/μCi retained) for the chair, H8, and L8SXB are shown in Figs. 87-89. The microcuries retained are calculated from excretion data. The chair calibration decreases ~20% in the first ~2 days and then remains essentially constant over the observation period of ~24 days. There is no significant difference between males and females. The average value is (80 ± 3%) cpc/μCi retained for the 1.00-MeV peak only and is consistent with a value of ~200 cpc/μCi retained from the phantom data which should be ~2 times greater because it includes both the 0.77- and 1.00-MeV peaks. The calibration factors for H8SXB and L8SXB both show the difference between the sexes as indicated above, with the females having the higher values. For the H8SXB position, the average value is (80 ± 3%) cpc/μCi retained for females and (50 ± 4%) for males. For the L8SXB position the respective values are 1150 ± 3% and 720 ± 5%. The factors for the H8SXB position during the first day increase by 25-30%.

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Table 39. The complete excretion results are summarized in this table which show that Th is excreted predominantly in the urine. The cumulative and daily urine excretion is about the same for males and females. The males excrete more Th in the feces leading to a urine to feces ratio which is ~2 times smaller than that of the females (~10 vs. ~20) for a 5-day accumulation. The reason for this sex difference (a difference which is further manifested by body measurements as described in the text) is not known. The urine-to-feces ratio takes several days to stabilize, starting out with higher values.

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Table 39. Excretion of Th^{234} by Human Beings Following Intravenous Injection

Subject	Time after Injection (Days)	Daily Urine %	Daily Feces %	Cum. Urine %	Cum. Feces %	Cum. Total %	Cum. Urine / Cum. Feces
TIVM2	1	3.28	0.00	3.28	0.00	3.28	-
	2	0.52	0.00	3.80	0.00	3.80	-
	3	0.54	-	4.34	0.00	4.34	-
	4	0.29	0.40	4.63	0.40	5.03	11.6
	5	0.27	-	4.90	0.40	5.30	12.2
	11	0.11					
	16	0.14					
	17	0.13					
	24	0.083					
IVM3	1	3.69	0.019	3.69	0.019	3.71	194.
	2	0.86	0.22	4.55	0.24	4.79	19.0
	3	0.66	0.10	5.21	0.34	5.55	15.3
	4	0.50	0.13	5.71	0.47	6.18	12.1
	5	0.25	-	5.96	0.47	6.43	12.7
	11	0.21					
	18	0.17					
	24	0.13					
TIVM5	1	2.74	0.00	2.74	0.00	2.74	-
	2	0.70	0.10	3.44	0.10	3.54	34.4
	3	0.40	0.12	3.84	0.22	4.06	17.4
	4	0.36	0.10	4.20	0.32	4.52	13.1
	5	0.25	0.043	4.45	0.36	4.81	12.4
	11	0.12					
	16	0.099					
	24	0.027					
TIVF2	1	4.11	0.034	4.11	0.034	4.14	121.
	2	0.68	0.032	4.79	0.066	4.86	72.6
	3	0.40	0.044	5.19	0.11	5.30	47.2
	4	0.21	0.094	5.40	0.20	5.60	27.0
	5	0.25	0.041	5.65	0.24	5.89	23.5
	10	0.17					
	17	0.10					
IVF3	1	4.11	0.020	4.11	0.020	4.13	206.
	2	0.83	0.084	4.94	0.10	5.04	49.4
	3	0.50	0.053	5.44	0.16	5.60	34.0
	4	0.39	-	5.83	0.16	5.99	36.4
	5	0.31	0.031	6.14	0.24	6.38	25.6
	10	0.19					
	17	0.090					

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Fig. 90. Retention of Intravenously Administered Th^{234}.

The retention results shown are compiled from several sets of measurements. The legend in the figure indicates these different measurements and their associated errors. The data are presented in an expanded log scale to show detail and as a consequence the chair and L8SXB results appear erratic. The variations in these data are not inconsistent with their standard deviations. The average curve shown is a composite for all subjects and of all the information available. The retention decreases to ~92% in ~15 days and remains essentially constant over the remaining ~110-day observation period. The retention half-period ranges from a minimum of ~2 years to ∞.

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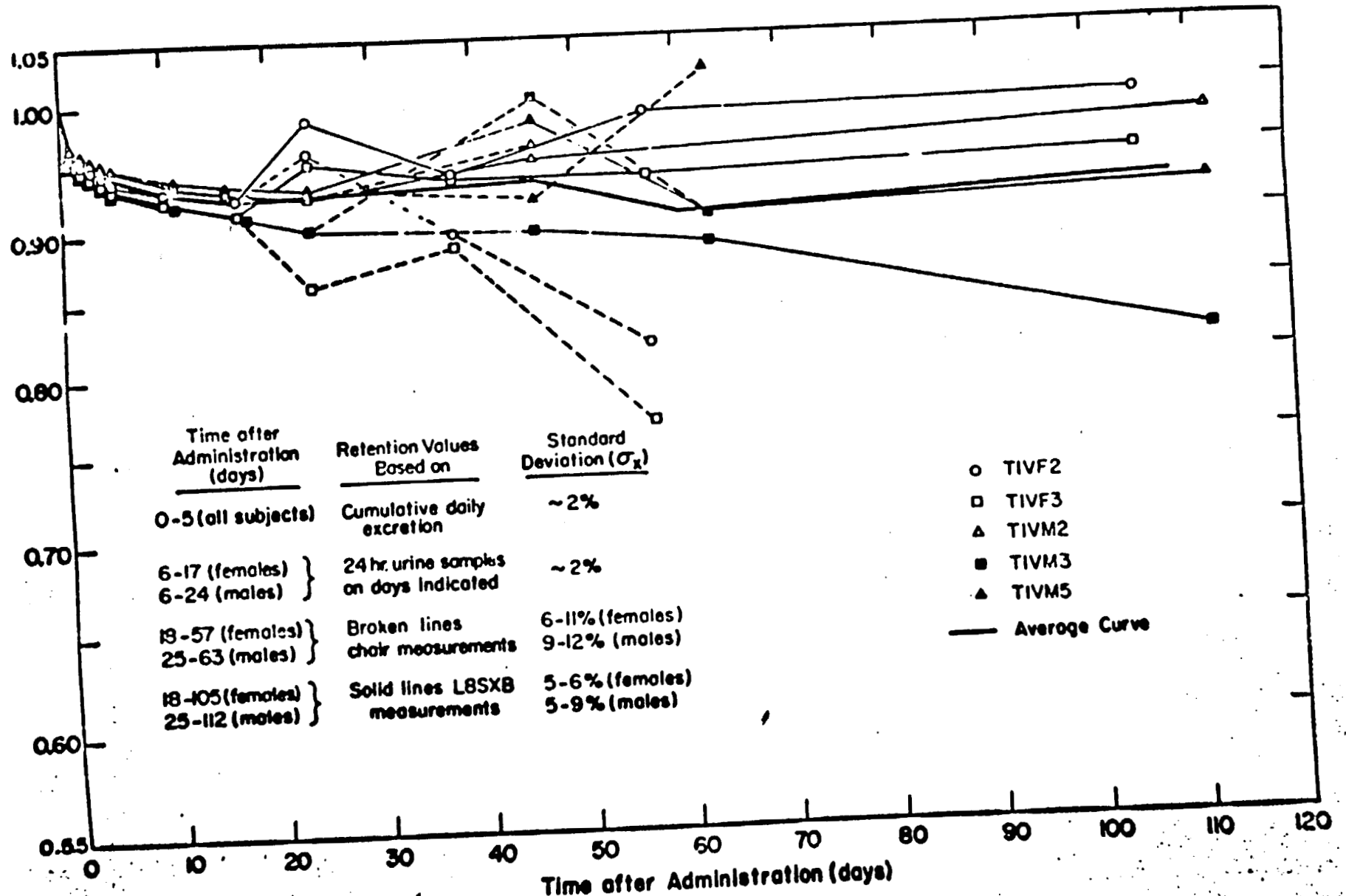
1.05
1.00
0.90
0.80
0.70
0.60
0.55
0
10
20
30
40
50
60
70
80
90
100
110
120
Time after Administration (days)
Time after Administration (days)
Retention Values Based on
Standard Deviation (σ_x)
0-5 (all subjects)
Cumulative daily excretion
~2%
6-17 (females)
6-24 (males)
24 hr. urine samples on days indicated
~2%
18-57 (females)
25-63 (males)
Broken lines chair measurements
6-11% (females)
9-12% (males)
18-105 (females)
25-112 (males)
Solid lines LBSXB measurements
5-6% (females)
5-9% (males)
TIVF2
TIVF3
TIVM2
TIVM3
TIVM5
Average Curve

Fig. 90.

Fig. 91. Th^{234} in Estimated Total Blood Volume Following Intravenous Administration.

The results are given in terms of total blood volume since there is no convenient way to express a thorium specific activity. The Th activity decreases over 2 decades in a period of 10 days. This rate of decrease is considerably slower than that for Ra. The last value of TIVMS has an error of ~100% and is plotted for the record.

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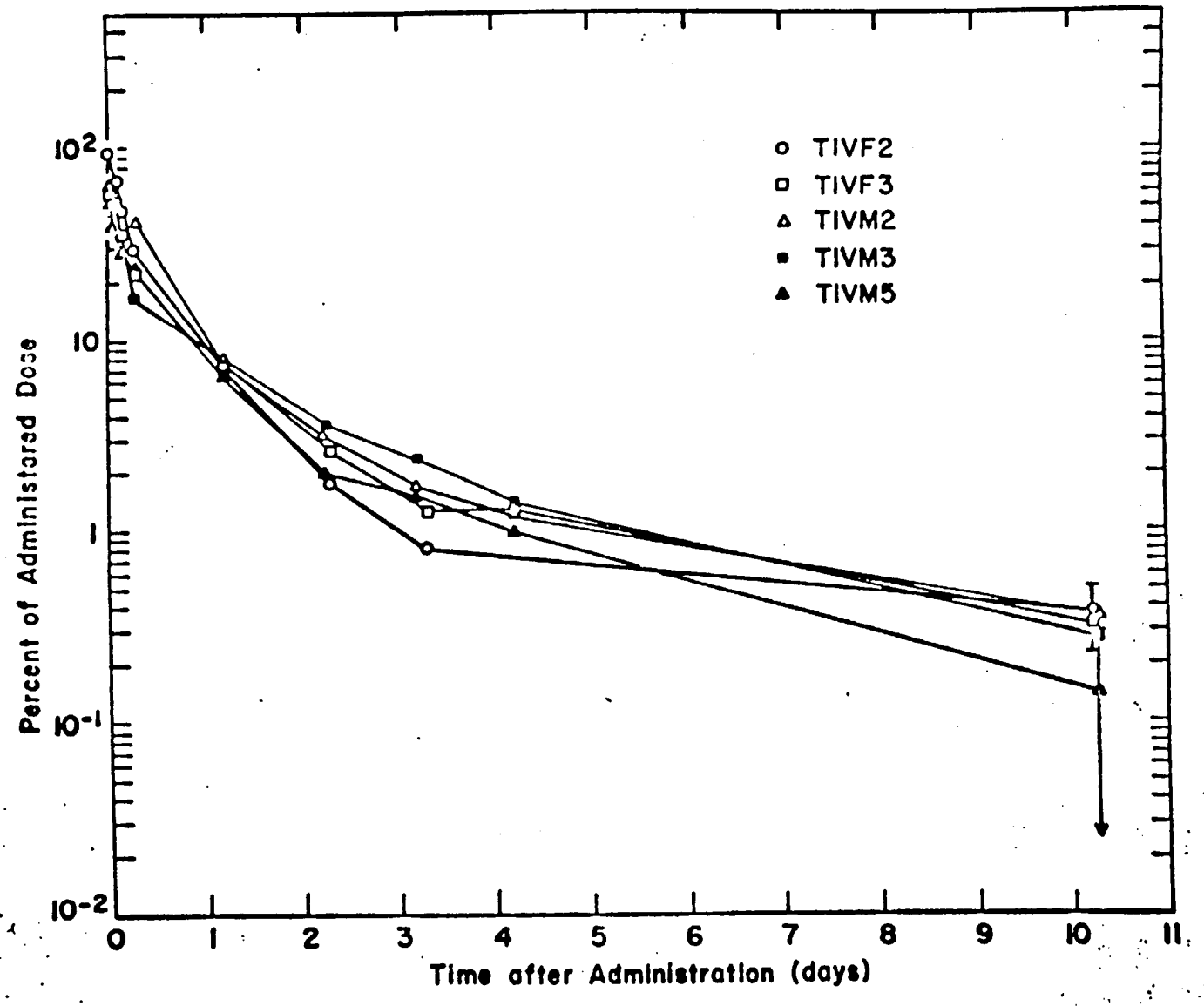

Fig. 91. Th^{234} in Estimated Total Blood Volume Following Intravenous Administration

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A discussion on the metabolism of intravenously injected Th^{234} in man becomes somewhat difficult from this limited information. In general, the results are comparable with those obtained on dogs by the Utah group[13]. The total excretion is less than for dogs, and the urine-to-feces ratio of 10-20 is greater than that for dogs. The urine-to-feces ratio decreases with time for dogs (not including a further decrease due to radiation damage by Th^{228} to the kidneys) but there is no information in human subjects bearing on this matter. The absolute retention for human beings is greater but the change in retention with time may be about the same. In dogs the soft tissue retention is ~20% of the total burden, but this fraction is unknown for human beings. The blood activity decreases less rapidly than for dogs. Some of these differences may be due to the fact that in the Utah dog experiments the number of Th atoms administered are several thousand times those administered to the human subjects of this study. There are enough differences between species [including the results on rats, rabbits, guinea pigs of Hamilton[57] and Scott[58]] to indicate that no simple extrapolation can be made to man. The present data provide some of the first results in human beings which contribute to the calculation of maximum permissible levels of Th nuclides in man but it is clear that the data are not extensive enough. There are some aspects of the present data that are not easily interpreted, but may point to redistribution within the body. This result indicates the need for tissue sampling (which is never convenient) or the need for scanning (which is difficult because of the low abundance of the γ rays). For more extensive data, Th^{234} is too short-lived. Yet the next longer-lived isotope is Th^{228} which is potentially toxic, and the measurement of which is complicated by the metabolism of its daughter, Ra^{224}.

An attempt to determine the localization of Th^{234} in the livers of these subjects was made by measurements in the arc position using an 8 in. thick lead shield extending 12 in. from a point halfway between the collar bone and the sternum towards the abdomen. The results in Table 40 show a reduction in Th^{234} activity to 0.74 indicating no significant disproportionate concentrations of Th^{234} in the shielded portion of the body

57. J.G. Hamilton, "The Metabolic Properties of the Fission Products and Actinide Elements", Rev. Mod. Phys. 70, 718-720 (1948).

58 J.K. Scott, W.F. Newman, and J.F. Bonner, "The Distribution and Excretion of Thorium Sulphate", J. Pharmacol. Exp. Therap. 106, 286-290 (1952).

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which includes the liver and spleen. The greater reduction in Ra^{224} activity to ~0.6 is explained by the presence of significant amounts of Ra^{224} activity in the G.I. tract during the first few days after injection, a situation which does not occur for Th^{234}.

The adequacy of the arc measurements is shown in Table 41. In contrast to the results on Ra^{224}, there appears to be a trend with time, where the arc measurement on the 1st day underestimates the body burden and on the 2nd and 4th days overestimates it. This effect may be due to the same type of redistribution observed for the other counting positions, but it is difficult to understand since the arc measurements on a highly distorted distribution even for Th^{234} (such as a swallowed capsule containing activity, subject TPO'il) can be close to the correct body burden. Nevertheless, this is the fact and the conclusion is that the body burden of Th^{234} obtained by any arc measurement is reliable to only ~±15%.

c. Results and discussion on the relative absorption of Ra^{224} and Th^{234} administered orally.

Having obtained information on the metabolism of Ra^{224} and Th^{234} and on the calibration factors derived from these results, pilot experiments were conducted to assess the problems to be encountered and to get an estimate of the absolute absorption by means of the oral administration of Ra^{224} to one subject and of Th^{234} to another. In particular, it was necessary to show that the shielding for the SXB positions, when large amounts of activity were in the stomachs of people (as opposed to phantoms), was adequate; to show the extent to which scattering of γ rays might influence the SXB positions especially the LB positions; to see how much time was required to eliminate the bulk of the activity from the G.I. tract and whether a good accounting of the total activity was obtainable; to see if the absorption calculated from the several parameters gave the same answer; and to determine whether the precautions did prevent radioactive contamination.

The two pilot experiments demonstrated that everything worked favorably and this information is included later with the results from the main study. The adequacy of the shielding for Th^{234} can be shown only when it is administered separately. The results are given in Table 42.

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and show that the H3SXB method meets the attenuation requirements originally specified. Scattering in the 1.00-MeV region for Th^{234} is presumed to be observable from the few higher energy γ rays of the Th^{234} daughters because the contribution decreases after the first day. On the other hand, scattering is noticeable in the L8SXB measurements and interferes for the first few days while significant activity is still present in the G.I. tract.

The pilot experiment on Ra^{224} also showed that the absorption of Ra^{224} is ~10 times greater than the ~1% assumed from previous information. This result pointed to the success of the experiment in the determination of the low relative absorption of Th to Ra, but showed that no meaningful L8SXB measurements could be made for Th^{234} within a few days after the administration. Thus, while much information was developed in the intravenous part of the experiment, Ra^{224} body γ measurements for the oral part of the study were done with the H3SXB position soon after administration. The Th^{234} body γ measurements were done with the L8SXB position long after the Ra^{224} had decayed, and this was possible because of the high Th^{234} retention.

Absorption from the gut (that is, the transport of material from the gut to the blood, irrespective of what happens to this material after it gets in the blood; otherwise called cumulative absorption) can be measured in many ways such as: (1) balance techniques with stable material, (2) balance techniques with radioactive material when endogenous excretion is known, and (3) radioisotope methods using the blood activity obtained from both oral and intravenous administration. The latter technique [described, for example, by Silverman and Burgen[59]] is particularly useful for carrying out an experiment over a relatively short period of time.

The information contained in the blood curves, obtained from an intravenous and a per os administration, is the same even though the two curves are different at short times after the administration. Following administration, and for times which are long compared with the period involved in the absorption process, the two curves become essentially equal in magnitude and identical in shape, on a per μCi retained basis. This condition is similar to the situation encountered for the relative activities between a short-lived daughter isotope and a long-lived parent. At any time (days)

59. M. Silverman and A.S.V. Burgen, "Application of Analogue Computer to Measurement of Intestinal Absorption Rates with Tracers", J. Appl. Physiol. 16, 911-913 (1961).

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long after the absorption is complete (~5-10 hours) the respective activity curves from the two methods of administration for all the various parameters (blood, urine, feces, whole body, etc.) will be indistinguishable from each other. At these times, the data obtained from the intravenous administration can be used as calibration data for determining the amount of material that was transported across the gut wall or absorbed after the oral administration. As a further check on this, several consecutive measurements of each variable, after the appropriate delay, should give the same value of absorption within the experimental error. And finally, the same absorption value should be obtained from each of the different variables measured, again within the experimental error.

The absorption of Ra^{224} was determined by measurements made from the 4th day on until radioactive decay prevented further reliable measurements. The adequacy for this procedure is shown in Figs. 92 and 81b obtained from a subject administered mock Ra paint containing only Ra^{224}. Figure 92 shows that relative stabilization in the body measurements does not take place until ~4 days after the Ra^{224} is administered. By this time the transitory effects of absorption from the G.I. tract have become negligible. This is shown in Fig. 81b where the first blood value taken at 1.12 hours after the administration has the highest value; that is, the peak in the blood curve occurs at $t \leq 1.12$ hours. This blood curve has the same shape as the blood curves from the experiments with the intravenous injections. The blood results obtained from the subject administered mock Ra paint containing only Th^{234} were too low to deduce a reliable shape for the curve.

The results from the oral administration of mock Ra paint containing both Ra^{224} and Th^{234} are shown in Tables 43-46. Table 43 contains the excretion and retention results and shows confirmation of the amount administered and the adequacy of the accounting of the radioactive balance. There is an apparent inconsistency for some subjects on days 1 and 2, attributable possibly to the distribution of the activity in the body, as noted in the footnote of the table. Of particular interest is the observation that essentially all the Th^{234}, a negligible amount of which crossed the gut wall, is excreted in ~4 days. This result is similar to that obtained by Hayes et al.[60] who administered insoluble La^{140} to a group of human subjects.

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Tables 44 and 45 show the results separately for Ra^{224} and Th^{234} respectively, as obtained from the several metabolic parameters. On the average, the results on both Tables 44 and 45 agree with each other within a factor of ~2. The results show that the values of fractional absorption calculated from the several parameters are consistent. The conclusion can also be made that no significant contamination has taken place for any particular sample or sample type.

One exception to this is the result on the absorption of Th^{234} obtained from the blood values. The blood samples were taken soon (2 and 5 hours) after the administration in order to observe some significant activity above background before metabolic activity reduced the Th^{234} concentration below the detection limit. The absorption calculated from blood samples taken at this early time (using the method of calculation described above) will underestimate the true value as the results in Table 45 indicate. These results confirm that Th^{234} was absorbed into the blood but cannot be and are not used for calculation of the average absorption.

Average values of fractional absorption or transport have been calculated from Tables 44 and 45 for Ra^{224} and Th^{234} for each subject and these results are shown in Table 46.

The fractional Th absorption or transport averages $\leq 3 \times 10^{-4}$ with a most probable value of 2×10^{-4}. A difference in absorption due to sex is not indicated. The results of the Utah animal experiments indicate that the absorption of Th is equal to and as much as 10 times less than that for the human subjects.

The fractional Ra absorption averages 0.2 with a most probable value of 0.2. Again, there is no sex difference indicated.

The first male subject, TRPOM1, has a fractional Ra absorption of ~0.01, about 20 times less that of the other subjects. This difference is real since the values of absorption calculated from the different parameters are consistent (Table 43). This discrepancy was resolved by a reexamination of the clinical status of this subject. At the suggestion of a colleague,* a routine gastric analysis before and after a test meal was made. The results showed no HCl in either specimen, indicating a condition of achlorhydria. With this condition, it would be expected that

*Dr. Roy E. Albert, Institute of Environmental Medicine, N.Y.U., Tuxedo, New York.

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Table 44. The results of the three methods for measuring Ra^{224} transport across the gut are shown. The [illegible] and breath results are in adequate agreement. The values obtained from urine measurements are somewhat lower but the error in these values is much greater. The results for the first case, TRPO:1 (based on the data which are internally consistent) are lower than for the others. These lower results are presumably due to the condition of achlorhydria found in this subject after the experiment was completed. From breath measurements in the first 2 days conducted only on the females, there are indications that the transport values of Ra^{224} determined from the breath Tn results at $t \leq 3$ days are higher than those determined at $t > 3$ days. This observation means that relatively more Tn is in the blood stream at these early times. Since the Ra^{224} was ingested, an explanation for this could be the direct transport of Tn across some point in the G.I. tract, as shown for Rn by Hursh et al.[61]

Table 45. The three methods of measurement indicate adequate agreement. From the results for TRPO:1, it is not known whether the transport of Th^{234} across his gut is much lower than that of the others, as is his transport of Ra^{224} shown in Table 44.

Table 46. The results for the transport of Ra and Th are based on the average values calculated for each individual from the results given in Tables 44 and 45. The most probable values for Ra and Th transport are obtained by omitting subject TRPO:1 who had an anomalous Ra transport value. The most probable value of the relative absorption of Th to Ra is $\sim 10^{-3}$.

61. J.B. Hursh, D.A. Morken, T.P. Davis, and A. Lovaas, "The Fate of Radon Ingested by Man". Health Physics [illegible]

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Table 44. Fractional Transport Across the Human Gut of Ra^{224} in Simulated Ra Dial Paint

Subject	Parameters		
	Body γ meas. [illegible]	Breath Rn	Urine
TRPOM1	≤0.014	0.007	≤0.06
TRPOM2	0.21	0.18	0.16
TRPOM3	0.14	0.18	0.09
TRPOF1	0.20	0.18	0.13 ± 0.07
TRPOF2	0.18	0.23	0.13 ± 0.07
TRPOF4	0.27	0.28	0.21 ± 0.08
Averages*	0.20	0.21	0.14

*Including TRPOM1.

Table 45. Fractional Transport Across the Human Gut of Th^{234} in Simulated Ra Dial Paint

Subject	Parameters		
	Body γ meas. LBSXB	Urine	Blood
TRPOM1	≤0.0003	≤0.0006	≤0.0001
TRPOM2	0.0006	0.0009	0.0003
TRPOM3	≤0.0003	0.0003	≤0.0001
TRPOF1	0.0002	0.0002	0.0003
TRPOF2	≤0.0001	0.0003	0.0001
TRPOF4	0.0002	0.0008	0.0001
Averages*	≤0.0003	≤0.0005	≤0.0002

*Including or excluding TRPOM1.

Table 46. Relative Absorption by Human Beings of Th and Ra in Simulated Ra Dial Paint

Subject	Fractional Th Transport	Fractional Ra Transport	Relative Absorption Th/Ra
TRPOM1	≤0.0003	0.01	≤0.03
TRPOM2	0.0006	0.2	0.003
TRPOM3	≤0.0003	0.1	≤0.003
TRPOF1	0.0002	0.2	0.001
TRPOF2	0.0001	0.2	0.0005
TRPOF4	0.0002	0.3	0.0007
Averages*	≤0.0003	0.2	≤0.002
Most probable value	0.0002	0.2	0.001

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the gelatin capsule and the ZnS might not be digested by this subject as efficiently as by a normal person and that the transport of the radioactive materials could be significantly lower.

The fractional Ra absorption of 0.2, obtained from a supposedly "insoluble" material, is much larger than those of the Utah animal experiments by as much as 2-3 orders of magnitude. The value of 0.2 is in agreement with the value of 0.2 found in the dog experiment conducted as a preliminary to the experiments on the human subjects. The value is about the same as that calculated from human subjects ingesting Ra from drinking water and foodstuffs. Using the data of Lucas[62] on the Ra^{226} body burden of normal human subjects and the Ra^{226} concentrations in their food and water intakes, an absorption of ~0.15 is calculated. This calculated absorption value applies to the condition when Ra^{226} in water is the primary source of Ra or when Ra^{226} in food is the primary source of Ra under circumstances where the Ra^{226} in water is extremely low. An absorption value in this domain can be calculated from the data of Soil et al.[11] for a male subject (age ~33 years) ingesting a "radium solution" (presumably $RaCl_2$). Several values of absorption can be obtained from the results. However, the range is large (10-70%) and it is not possible to pick a reasonable average value.

The result of greatest interest, the relative absorption of Th to Ra is given in the last column of Table 46. Except for the first subject all the values are consistent, yielding a most probable value of 1×10^{-3}. This value is 10 times lower than the value discussed in the beginning of the paper where it was indicated that a value of 10^{-2} would be a desirable limit for disregarding the dosimetric effects from any Th^{228} present in Ra dial paints.

The absorption of Ra from the insoluble $RaSO_4$ (with Ba carrier) deposited on the ZnS phosphor is quite large. The absorption of Ra under the best circumstances of full solubility cannot be more than 5 times greater than the 0.2 found and very few substances are absorbed 100% from the G.I. tract. The high value of 0.2 would indicate that most,

62. H.F. Lucas, "Correlation of the Natural Radioactivity of the Human Body to that of its Environment: Uptake and Retention of Ra^{226} from Food and Water", ANL-6297, pp. 55-56 (July-Dec. 1960).

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argument, however, gives no clue as to how much more the Th might be absorbed but suggests that it might not be too much greater.

In the applicable experiments at Utah, the Th/Ra skeletal retention ratio in the rat at 10 days after administration of chloride and citrate solution is ~0.07 and ~0.004, respectively. However, this ratio is ~14 when mock Ra dial paint is administered. These results, therefore, cannot be used to deduce or estimate how large the absorption of soluble Th might be in human beings.

The Ra dial paints used in the early 1920's were made in a variety of ways and with varying degrees of care. In many or even most paints, the soluble activities were not washed off. Various and varying compounds were used for the matrix to make the paint adhere to the different surfaces on which it was applied. Varying screen sizes and clumping after drying, along with varying ages of the paint, all introduce variables for absorption. The radiation dose from the α rays may also have an effect on older paint that freshly made paint might not encounter. Thus, it is impossible to duplicate the original paints in their final working form, and in the extent to which "soluble" activities were present. Finally, even the subjects cannot be reproduced, since the dial painters were young girls usually in their late teens and early twenties as compared with the older subjects who participated in this study. All these are variables that make it difficult for a study conducted today to duplicate the conditions of the past and that make interpretations of present experiments complicated.

It is interesting to note that the absorption values used for Ra and Th in NBS Handbook 52 (March 1953) are 0.2 and 5×10^{-4} respectively, presumably for soluble salts. The Ra value is the same as that found in this experiment for an "insoluble" paint, while the Th is only ~2-3 times larger. The more recent values used for calculating the maximum permissible concentrations for NBS Handbook 69 (June 1959) are found in the ICRP Report Committee II on Permissible Doses for Internal Emitters (1959) and are 0.3 and $<10^{-4}$, respectively. These absorption values are based mainly on the literature of the 30's and 40's and are derived and estimated from animal experiments.

In view of the goal of finding a relative absorption of Th/Ra $\leq 10^{-2}$, and in view of finding a value of $\sim 10^{-3}$, it is concluded that, even in the

face of the limitations enumerated above, the absorption of Th^{228} (present in amounts up to equilibrium with its parent Ra^{228}) from real dial paints is unlikely to have been large while dial painters tipped their brushes in the 1920's. In these subjects the contribution to the integrated radiation dose over 30-40 years by the initially absorbed Th^{228} is ≤5% that due to Ra^{228}.

On the basis of this conclusion, comparison between the effects of Ra^{228} and Ra^{226} in human beings with these burdens can be continued using the concept of pure radium equivalent (PRE). On the other hand, use of the concept of minimum pure Ra equivalent (MPRE) can be discarded with reasonably good confidence.

Acknowledgements

The main portion of this report, namely the relative absorption of Ra and Th, has been "on the books" for many years. The importance of ([8] as a possible source of internal radiation dose became evident when Ra^{228} was rediscovered[4] in the late forties and early fifties to have been ingested in large quantities by many Ra dial painters. (Dr. Harrison Martland discussed Ra^{228} in dial painters in his early papers; however, attention was directed on Ra^{226} while Ra^{228} fell by the wayside for a while.) The effects of Th^{228} were implicit in the planning of the experiments on dogs which are being conducted by the Radiobiology Laboratory of the University of Utah. The formal discussions on this phase of Ra toxicity appear in the second annual conference of this group[8], including discussions to plan an experiment on the relative absorption of Th^{228} and Ra^{226} on animals. The results of these experiments, conducted in the following years, are described in the introduction of the present report. As time progressed, however, it was felt that the most believable answer would come from experiments conducted on human beings. In 1960, R. A. Dudley prepared a short protocol for such an experiment[9] and work was finally started in 1961. Over the years, then, many persons have had a hand in planning the experiment or in presenting their views on different phases (:.

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