UNRESOLVED PROBLEMS ASSOCIATED WITH EVALUATION OF TISSUE DOSE FOR THE THOROTRAST PATIENT GROUP*

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Abstract—With the intent of enabling a more precise specification of radiation dose to Thorotrast-injected patients, a study has been made of the physico-chemical properties of Thorotrast solutions. This study has focussed on the tendency of ^{232}Th daughters to adsorb on glass of the vials in which Thorotrast is dispensed by the manufacturer. It has been found that 50 to 90% of ^{228}Ra and ^{228}Th daughters adsorb when ultracentrifugation experiments show them to exist as polymers in the solution. It has not been possible to relate the tendency to form aggregates to pH, age of the solution, or concentration of the daughters. It is shown by calculation that the maximum uncertainty of radiation dose (15-year interval of exposure) may be as much as 50 per cent due to inability to specify the daughter content of the injected Thorotrast.

INTRODUCTION

Thorotrast is an aqueous suspension of thorium dioxide widely used by radiologists as an X-ray opaque medium during the period 1930 to 1945. Since then its use has been greatly curtailed because of a significant incidence of injection site sequelae and because of the recognition of potential late radiation injury to the injected patient. The existence of a sizeable group[1] of living subjects who have borne a low level radioactive burden for 20–35 years creates a challenge for the radiation biologists to relate the late injury effects with the radiation dose. In contrast to the radium dial painter group who acquired their burden by occupational exposure, this group of Thorotrast patients present three unique advantages. The range of thorium burdens is relatively small since standard volumes of Thorotrast were customarily used for a particular diagnostic procedure. Secondly, in many cases, the amount of Thorotrast used and date of injection can be obtained from the hospital records. Thirdly, the radiation exposure is presumptively an exposure of the reticulo-endothelial system, expanding the information gained from the radium group, for which the skeleton was the radiation target. To oppose to these advantages radiation dose calculation for Thorotrast subjects presents some special problems. These problems may be considered as: (1) specification of the ^{232}Th daughter-product content of the injected suspension; (2) determination of self-absorption of alpha emissions in the Thorotrast particles, particularly since large aggregates tend to form in the reticulo-endothelial system; and (3) the study of the fate and body distribution of the long-lived thorium daughters. Since categories 2 and 3 have been considered elsewhere,[1, 2] the present paper will report experimental data bearing on the first problem area. Several investigators have noted[3, 4] the tendency for the long-lived daughters ^{228}Ra and ^{228}Th (Fig. 1) to adsorb on the glass walls of the vial supplied by the manufacturer. Accordingly, even though the volume of Thorotrast injected may be known, the daughter content may be uncertain. The retrospective reconstruction of the total radiation dose sustained

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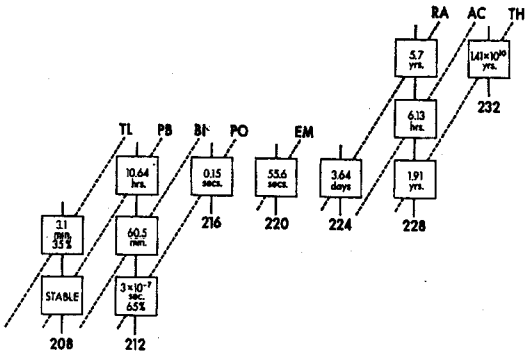

FIG. 1. Thorium decay scheme.

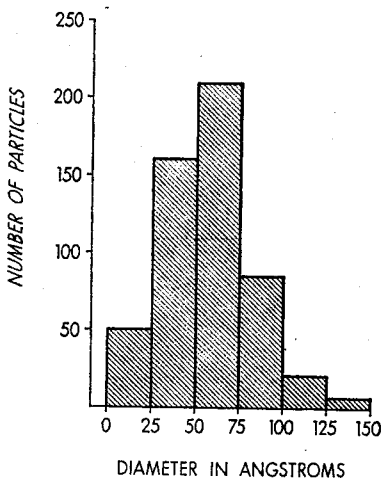

FIG. 2. Data obtained from electron microscope study of Thorotrast particle size.

is therefore subject to error. In the following we shall consider the physico-chemical properties of Thorotrast as related to thorium daughter behavior and shall inquire as to whether a likely daughter-product content of the injected material can be discovered.

GENERAL PROPERTIES

Thorotrast is a brownish colored, opaque, freely flowing suspension labeled as containing "24% to 26% stabilized colloidal Thorium Dioxide; 25% aqueous Dextrin; 0.15% Methyl Parasept as preservative". On each bottle an expiration date (month, day, and year) appears, set ahead five years from date of packaging into vials. This practice is probably[5] not related to expected instability of the suspension due to aging but more likely associated with the increased radioactivity of the material as the long-lived daughter ^{228}Ra increases with time after the chemical separation of thorium.

Rundo[6] quotes Johansen as authority for the statement that Thorotrast produced in the United States contains 0.22 g ^{232}Th per ml and, in Germany, 0.195 g ^{232}Th per ml. Analysis by us of Thorotrast manufactured in the United States yielded 0.22—0.23 g ^{232}Th per ml. The specific gravity is found to be 1.3 g ml. The size of the suspended thorium dioxide particles has been measured by use of an electron microscope in this laboratory[7] and by others.[8] The data obtained by us is plotted in Fig. 2. The photographs used for the particle measurement show them as roughly spherical in shape. The average diameter is 55 $\pm$ 25A°.

DAUGHTER PRODUCT CONTENT OF THOROTRAST VIALS AS PREPARED FOR USE

It is usually assumed that thorium-bearing ore contains the thorium daughters in equilibrium by virtue of its age. The chemical separation of thorium in the refining process segregates ^{232}Th and ^{228}Th from the long-lived ^{228}Ra and, less significantly, from the remaining short-lived daughters. The change in ^{228}Th and ^{228}Ra content of the thorium salt subsequent to chemical separation can be predicted by reference to details of the decay chain (see Fig. 1) and application of the Bateman equations yielding the result shown in Fig. 3.

If a single chemical separation is postulated and if no preferential loss of ^{232}Th, ^{228}Ra, or ^{228}Th occurs during processing of the thorium salt, it would be expected that Thorotrast as prepared for use would have parent-daughter relationships according to Fig. 3.

Three lots of Thorotrast available to us have been analyzed for daughter content using gamma spectrographic measurement techniques. Lot A subsequently referred to as "fresh" Thorotrast included six vials measured four months after packaging; Lot B and Lot C, subsequently referred to as "aged" Thorotrast, included 3 and 4 vials respectively and were measured 5.25 and 5.75 years after packaging. The average value and standard deviation is plotted

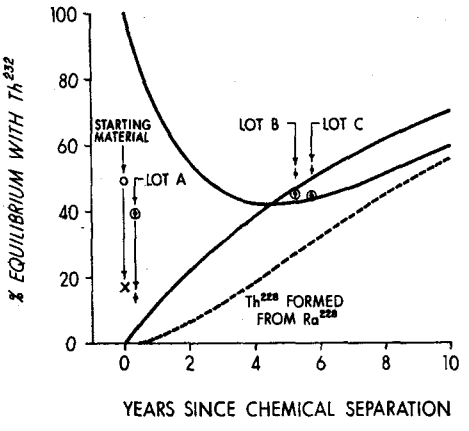

FIG. 3. Calculated curves to show growth of ^{228}Th (concave curve) and ^{228}Ra (convex curve) in a closed system, assuming that at $t = 0$, ^{228}Th is at 100% activity equilibrium with ^{232}Th and ^{228}Ra is zero.

in Fig. 3 with the abscissa taken as the packaging to measurement time interval.

All three sets of points indicate that the last chemical separation took place some time before product packaging and, indeed, the description of the manufacturing process[9] indicates that this interval is no less than 6 months and may be in excess of a year, depending on the age of the thorium oxalate used as a starting material. However, even if each set of points is shifted to the right so that the ^{228}Ra value falls on the predicted line, the ^{228}Th activity for the "fresh" Thorotrast is only about 50% of that predicted. This is interpreted to indicate that during the processing of the ore and the preparation of thorium oxalate several chemical separations took place over a period of some years, and that at each separation radium was removed so that the period of growth yielding the measured ^{228}Ra activity is much shorter than the time during which the ^{228}Th, initially at equilibrium in the ore, has decayed. Qualitative evidence to support this comes from an analysis of a sample of thorium oxalate used as starting material by the Testagar Company, producers of Thorotrast. The ^{228}Ra and ^{228}Th values for the oxalate are included in Fig. 3, and show a similar ^{228}Th deficiency.

EFFECT OF THOROTRAST TRANSFER ON DAUGHTER-PRODUCT CONTENT

The next set of experiments was to transfer the Thorotrast from its original container to a vial of identical size and shape. The empty vial as well as the vial containing the transferred material was measured by gamma spectroscopic techniques at appropriate times so that the transferred amounts of the various daughters could be determined. The results appear in Table 1 and indicate the completely different behavior of the daughters in the fresh and aged lot. Only about 1% of the daughters remained in the original vial for the fresh lot. A substantial fraction of this must have been Thorotrast solution incompletely drained from the vessel walls. For the aged lot 63 and 88% of the ^{228}Ra and 55 to 78% of the ^{228}Th remained adsorbed on the walls of the original vial. Radium-224 was estimated in each case and showed insignificant variations from ^{228}Th.

DAUGHTER CONTENT OF ULTRACENTRIFUGE FRACTIONS

Several experiments were performed in which 4 ml portions of the fresh and the aged Thorotrast were simultaneously centrifuged at 40,000 rpm for times from 3 to 5 hr at a force of from 84,000 to 175,000 g (depending on position in the centrifuge tube). The results obtained from a typical experiment (3 hr centrifugation) are shown in Fig. 4. The fractions A, B, C, and D were removed with the least possible disturbance of the contents and represent the top quarter, the second quarter, the third quarter, and bottom quarter of the centrifuged Thorotrast. They were then analyzed by gamma spectroscopy. It may be seen that fractions A, B, and C show no significant difference in concentration of ^{228}Ra and ^{224}Ra for the fresh Thorotrast. Fraction D shows an increase in concentration for ^{228}Ra and for ^{224}Ra of 65 and 12% respectively. The ^{228}Th presents a different picture and to a first approximation, appears to be distributed according to the ThO_2 content of the fractions. This is reasonable on the likely grounds that a major fraction of the ^{228}Th is in the form of the oxide and a relatively small amount (see Fig. 3) has been generated by ^{228}Ra decay taking place after the Thorotrast was sealed in the vial.

Table 1. *Daughters Adsorbed as Found by Transfer of Fresh (Vial Nos.* 2–6) *and Aged (Vial Nos.* 13, 14, *and* 15) *Lots of Thorotrast from Original Vials*

Vial No.	^{228}Ra content μCi			^{228}Th content μCi		
	Before transfer	After transfer	% Left	Before transfer	After transfer	% Left
2	0.0406	0.0005	1.2	0.112	0.0013	1.1
3	0.0398	0.0005	1.2	0.111	0.0014	1.2
4	0.0428	0.0006	1.3	0.117	0.0015	1.3
5	0.0402	0.0005	1.2	0.113	0.0015	1.3
6	0.0440	0.0004	1.0	0.119	0.0014	1.2
13	0.139	0.0880	63	0.122	0.0672	55
14	0.153	0.1330	87	0.138	0.108	78
15	0.144	0.1252	87	0.129	0.101	78

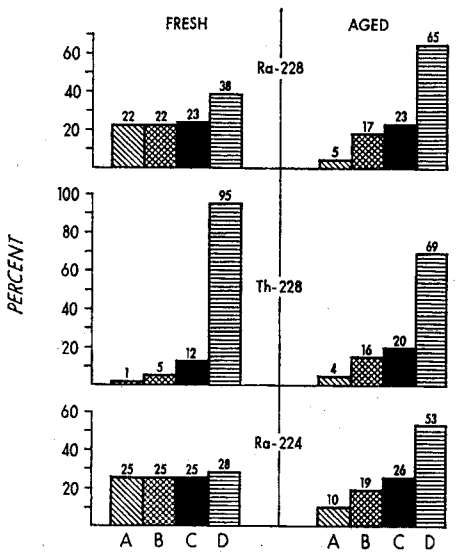

FIG. 4. Comparison of sedimentation in the fresh and aged lots of Thorotrast. Percent of thorium daughter per milliliter in ultra centrifuge fractions of increasing density gradient from A to D.

The fractional distribution of the aged Thorotrast shows a grossly similar pattern for all three daughters, indicating a considerable amount of sedimentation. The amount in each fraction appears to be nearly the same for ^{228}Ra and ^{228}Th whereas ^{224}Ra shows a somewhat greater concentration in the "lighter" fractions.

DISCUSSION

Taken together the transfer experiments and the ultracentrifuge experiments suggest that if the thorium daughters exist as small entities, probably in ionic form, they do not adsorb to the glass walls, whereas if they exist as polymers, they have a marked tendency to adsorb to glass. A similar tendency of polonium to adsorb on walls of the container has been related to the formation of polymers.[10] Although this situation is by no means well understood in physico-chemical terms, one may speculate that the low velocities and the tendency to become insoluble of the larger aggregates would predispose toward adsorption on glass. Any theory, and none will be presented here, would need to include an explanation of why the daughter aggregates do not adsorb on the Thorotrast particles themselves.

The question of more concern to the immediate study is, "Why do aggregates form in one Thorotrast suspension and not in the other?" The experience of investigators injecting animals with radium, as well as the studies with polonium,[10] is that adsorption occurs when the pH of the solution is near neutrality. We were not able to establish that the pH of the "fresh" versus "aged" lot varied in a significant way.

Eleven vials of the fresh lot measured from pH 6.03 to 6.22 whereas 3 vials of the aged lot measured from 6.02 to 6.40. No drift was noticed during measurement. If the result of the polonium study can be extrapolated to the present investigation, it might be supposed that, in terms of pH, conditions were suitable for formation of polymers in both "fresh" and "aged" lots.

Other conditions favoring the formation of aggregates would be the presence of foreign particles, concentration of daughters, and "age" of suspension. Our limited study does not permit identification of any of these factors as critical in producing the differences noted. An interpretation on grounds of relative "age" is not convincing since the important distinction would be expected to be on a time scale of days or weeks rather than years.

In summary we must present the conclusion that if the daughters exist in the Thorotrast suspension as aggregates, adsorption to the glass walls will occur, but that the critical condition bringing about aggregation in one lot and not in another lot remains unidentified.

PERTINENCE OF THIS STUDY TO DOSE CALCULATION

On the basis of these studies and other measurements an arbitrary opinion is presented that for the Thorotrast subject group the injected material contained ^{228}Ra in amounts from 2.5% to 35% of radioactive equilibrium with ^{232}Th and that the corresponding values for ^{228}Th were 15 to 40%. It is hoped that further study may improve on these estimates.

In order to justify such further effort, it is appropriate to consider what fraction of a total 15-year dose can be attributed to the injected ^{228}Ra and ^{228}Th daughters as contrasted with the fraction produced by daughters formed *in vivo*. The results of such a calculation are shown in Fig. 5 and the area for each curve (integrated from zero time to 15 years) is noted. In the simplified model used for calculation it is assumed that the ^{228}Th burden will be a sufficient measure of relative dose rate. The extreme values of ^{228}Ra at 35% and ^{228}Th at 40% have been used for the injected levels. It has been assumed that the excretion of ^{228}Ra will occur at 0.35% per day for the period 0 to

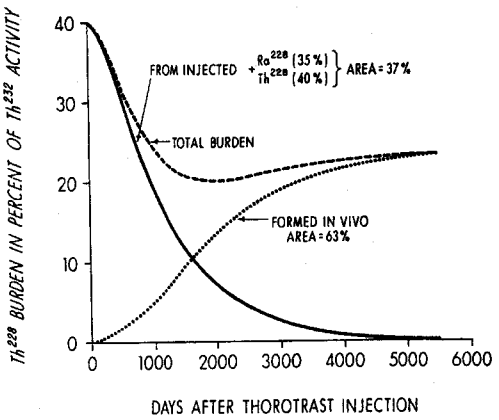

FIG. 5. Calculated curves of the ^{228}Th *in vivo* burden assuming injected amounts of ^{228}Th and ^{228}Ra are as stipulated.

700 days and at 0.1% per day for 700 days to 15 years after injection.[11] It is further assumed that the excretion of ^{228}Th is zero[12] at all times. A calculation done in this way stipulates that about one-third of the dose can come from the injected daughters. It should be understood that this is believed to be a maximum, and it is acknowledged that use of other plausible assumptions about daughter excretion rate and/or calculation for a longer exposure period would yield a lower estimate.

May I conclude this paper with an endorsement of the theme of Dr. Robert Dudley's presentation of Thorotrast dosimetry at the New York Academy of Science,[1] i.e. "Thorotrast dosimetry is complicated," and add the footnote that the thorium daughters begin to misbehave before they get out of the bottle.

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