THE DOSIMETRY AND TOXICITY OF THOROTRAST

A Scientific Meeting Organized by the
International Atomic Energy Agency
and the
World Health Organization

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FOREWORD

In October, 1965, a Meeting on the Dosimetry and Toxicity of Thorotrast was held in Vienna under the auspices of the International Atomic Energy Agency and the World Health Organization.

Thorotrast (a proprietary colloidal thorium dioxide preparation) was widely used as a radiographic contrast medium in the period 1930 - 1950. Since it is retained in the body over long periods of time, the persons thus examined now constitute one of the comparatively few population groups exposed to long-continued internal irradiation at a toxicologically interesting level. Numerous studies of these individuals have been initiated in many laboratories in the hope that valuable data on the response of humans to such irradiation might be collected. The purpose of this meeting was to review the available factual information on this subject, and to improve collaboration among the laboratories engaged in these studies.

The scientific papers presented at this meeting have been collected in this booklet. A number of them have been somewhat condensed or edited from a linguistic point of view, but the authors alone remain responsible for the opinions expressed.

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MANUFACTURE OF THOROTRAST

O. Wiedemann

The author has attempted to accumulate from the records of his firm, Chemische Fabrik von Heyden Aktiengesellschaft, and from discussions with its past and present staff members, the available information on thorium preparations used in medical practice.

1. History

At the beginning of this century the Chemische Fabrik von Heyden at Dresden-Radebeul did pioneer work in the chemistry of colloids. In collaboration with university institutions a series of chemical elements (e.g. silver, gold, iron and sulfur) and later also chemical compounds (e.g. silver chloride and silicic acid) were prepared in colloidal form and employed, among other applications, in the medical field. Heyden produced these colloids on a technical scale and was a leader in the field. In the 1920's Heyden extended its colloid chemical research to metal-oxides such as titanium oxide, ferrous oxide, chromium oxide and thorium dioxide. The latter seemed predestined as a contrast agent in X-ray diagnostics because of the high absorption coefficient of thorium for X-rays. In the late 1920's, after numerous clinical trials, Heyden placed the first colloidal thorium preparation, under the trade name of Umbrathor, at the disposal of radiologists.

Umbrathor was a non-stabilized thorium dioxide sol with a positive charge and with a content of 25% ThO_2 and pH 2.8 - 3. It flocculated with proteins, including those in the human body. Oral administration gave excellent contrast pictures of the gastric mucosa and the upper portion of intestines. Rectal administration provided a contrast picture of the large intestine. However, Umbrathor could not be introduced into the blood stream because of its sensitivity to proteins and its gross acidity.

At the suggestion of the Berlin University Hospital Moabit Heyden experimented with the preparation of a thorium dioxide sol which would be alkaline-stable and would not flocculate with body fluids. By use of protective colloids, such as semi-colloidal decomposition products of starch, this aim was reached and the stabilized preparation was marketed under the trade name Thorotrast in 1931 (25 % Th O_2, pH 8.1 - 8.3).

Thorotrast proved to be an ideal agent in radiography for demonstrating cavities and narrow canals. Furthermore, it could also be administered both intravenously and intraarterially. Excellent X-ray pictures of the liver and the spleen (hepatosplenography) were obtained after intravenous injection. After arterial administration, outstanding pictures of the brain (arterial encephalography) and also of the arteries of the limbs were obtained. In numerous publications the excellent clarity of the pictures was emphasized as well as the painlessness of administration. Prof. Moniz Lizzboa published several papers introducing Thorotrast to the medical profession.

Thorotrast became well established in the practice of radiologists, but already in the 1930's doubts about its safety were publicized. These were based on the findings that Thorotrast is not eliminated from the body after administration into the blood stream, but is deposited in the liver, spleen, and bone-marrow. Furthermore, doses up to 75 cc were necessary for hepatosplenography. In hospitals and practices after 5 years of use almost no serious injuries were known except for inflammations due to improper injections, or occasional discomfort with a rise in temperature. However, tests in rats and mice showed inflammation and shrinkage of the liver and the spleen after high doses. Later the carcinogenic effects of Thorotrast, many years after administration, became apparent.

After expropriation and the partial dismounting of the works at Dresden in 1945, and after the transfer of the company to Munich in 1949, we decided not to include this article in the production program of Heyden in West Germany. However, we received frequent requests for Thorotrast from scientific institutions which wanted to use this material for experimental purposes, so that after all we did produce some hundreds of 10 ml vials to meet their needs. However, in the catalogue, the dangers were pointed out, and there was a recommendation that the preparation should be used only in animal experiments.

Concerning the quantities of Thorotrast produced by Heyden at Dresden-Radebeul, we do not have complete or exact data. (Ed. note: Subsequent to the meeting, Dr. O. Wiedemann obtained from Dr. Koenig (Staatliche Zentrale für Strahlenschutz, German Democratic Republic) the partial and approximate figures for Umbrathor and Thorotrast production at Heyden in Dresden-Radebeul during the period 1939 - 1952. These data are shown in Table 1 in units of kg of pure Th O_2).

TABLE 1

Heyden production of Th O_2
for Umbrathor and Thorotrast,
Dresden-Radebeul

Year	kg pure Th O_2	Year	kg pure Th O_2
1939	600-800	1946	?
1940	600-800	1947	94
1941	600-800	1948	77
1942	?	1949	56
1943	839	1950	53
1944	868	1951	14
1945(Jan-May)	192	1952	19

2. Chemical preparation

Some of the early experience of the firm Heyden with Umbrathor and Thorotrast is described in the Heyden Year Book: pp. 95,99 (1931), p. 68 (1933), p. 57 (1934), p. 51 (1935), p.81ff (1938).

The pure thorium oxalate is manfactured from monazite sand by treatmont with concentrated H_2SO_4, repeated precipitation of the thorium as phosphate from the solution containing phosphoric acid by means of Mg O and addition of oxalic acid to the acidic solution (sulfuric acid) of the third phosphate precipitation (Patent DRP 580216 of June 23, 1932, Chemische Fabrik von Heyden, Dr. Zellmann and Dr. Richard Müller). The purification of thorium oxide is achieved by a cold and subsequent warm treatment with sulfuric acid (Patent DRP 591478 of June 23, 1932, Chemische Fabrik von Heyden, Dr. Zellman and Dr. Richard Müller).

Thorium dioxide is the result of the thermal decomposition of thorium oxalate. The physical-chemical characteristics of the so prepared thorium oxide depend on the time and temperature of the reaction:

(1) Above 600°: Insoluble in boiling hydrochloric acid and nitric acid; can be dissolved only by treatment with hot concentrated sulfuric acid.

(2) Between 500 - 600° (5 hours): Insoluble in concentrated hydrochloric acid and nitric acid, but gives a thorium dioxide colloid by treatment with diluted hydrochloric acid.

(3) 300° (24 hours): Soluble in HCl and HNO_3. Especially easily soluble if the decomposition of the oxalate is carried through in vacuum (Patents DRP 633 996 of July 30, 1936 and DRP 645 366 of December 23, 1937, Chemische Fabrik von Heyden, Dr. Richard Müller).

The sol prepared by method (2) can be stabilized against electrolytes and proteins by the use of colloidal and semicolloidal decomposition products of starch (Patent DRP 588 563 of November 19, 1929, Chemische Fabrik von Heyden, Dr. R. Zellmann).

Umbrathor is prepared according to the following method. The finely pulverized thorium oxalate is heated in a furnace for 5 hours. During this period the temperature is controlled to such an extent by blowing dry air through the reaction mixture, that even during the sudden onset of the exothermic reaction it remains between 525 - 530°. The oxide is digested with 1 1/2 times its amount of 0.2 N hydrochloric acid. (This is only a small part of the hydrochloric acid which would be necessary to prepare thorium chloride from the oxide). The preparation of the sol is accomplished by warming this solution for 8 hours in a water bath. The result is a fluid which is nearly completely clear in transmitted light but is milky in dispersed light. Umbrathor is prepared from this solution by sedimentation of the larger particles possibly present, and adjustment of the pH to 2.8 - 3.0 and the thorium oxide content to 25 %.

The preparation of Thorotrast (stabilized form of thorium oxide sol) is undertaken by mixing 10 parts of 50 % acidic sol (HCl) with 4 parts of dextrin in 5 parts of double distilled water. The pH of this rough mixture is adjusted with a solution of 25 % sodium hydroxide to pH 8.1 - 8.3 and the thorium dioxide concentration to 25 %. To preserve the sol, 0.15 % of p-oxibenzoic acid ethylester is added in a small amount of ethanol. The sol thus prepared is stored in CO_2-free atmosphere for several weeks and is then carefully decanted into ampoules. The ampoules

are sterilized by steam heat for 30 minutes. According to our experience the stability of this preparation is not unlimited. Samples older than one year have shown gel-like precipitations, turbidity and even the start of sedimentation.

THE RADIOACTIVITY OF THOROTRAST AND ITS IN VITRO DISTRIBUTION BETWEEN THE VARIOUS PHYSICAL PHASES

R. M. Parr

1. Introduction

The evaluation of the dose rate from deposits of Thorotrast within the human body is a notoriously difficult problem which still awaits a complete solution. Quite apart from the complicated metabolic behaviour of this substance there are a large number of purely physical parameters which are important in determining the dose rate that it produces in vivo. These can be discussed under two broad headings - firstly, the radioactivity that it contains, and secondly, the distribution of this activity between its various physical phases.

The first of these two subjects - although it involves complex considerations of the age of the Thorotrast and the previous history of the thorium from which it was manufactured - is well understood, and need be discussed only briefly here. The second is of no less importance, but at the present time it is more a field for speculation than for firm knowledge, and a great deal more experimental work is called for to clear up the many obscurities and contradictions that exist. The importance of understanding the mechanisms which determine the distribution of activities between the different phases of Thorotrast in vitro lies in the likelihood that they have an important bearing on the dosimetry in vivo of this material at early times after injection, and even up to 10 years later.

2. The radioactivity of Thorotrast

Between the parent nuclide Th-232 and the final stable nuclide in its decay series, Pb-208, there are a total of ten different radioactive daughters with half-lives ranging from 0.3 μseconds to 5.75 years (Table 1). Within a sealed container such as a Thorotrast ampoule, many of these grow rapidly into radioactive equilibrium with the parent nuclide from which they are derived. Thus on a time scale measured in months or years it is convenient to consider the series as comprising just three different nuclide groups (1) Th-232, (2) Ra-228 and Ac-228 in radioactive equilibrium, and characterized by the decay constant of Ra-228, and (3) Th-228 and subsequent daughter nuclides, all in radioactive equilibrium and characterized by the decay constant of Th-228.

The activity of Th-232 is a constant (except on a geological time scale) which can be evaluated by a simple calculation from the known chemical composition of the Thorotrast. The only important variables that need to be defined are therefore the activities of Ra-228 and Th-228.

Table 1

Physical characteristics of the decay of Th-232 and its decay series

Serial number of daughter nuclide	Nuclide	Half-life	Particle emitted and energy, MeV	Principal γ-ray energies [a]
0 (parent)	Th-232	1.4×10^{10} yr	α 4.01	none
1	Ra-228	5.75 yr	β 0.053	none
2	Ac-228	6.13 hr	β 1.11 and others	0.34; 0.97; others up to 1.64
3	Th-228	1.91 yr	α 5.42 (0.71), 5.34 (0.28)	none
4	Ra-224	3.62 days	α 5.68	0.241 (weak)
5	Rn-220	54.5 sec	α 6.28	none
6	Po-216	0.16 sec	α 6.77	none
7	Pb-212	10.6 hr	β 0.36	0.239
8	Bi-212	60.5 min	α (0.337) 6.05; β (0.663) 2.25	0.73 (weak)
9	Po-212	0.3 μsec	α 8.78	none
10	Tl-208	3.1 min	β 1.77	0.58; 2.62; and others

(a) Only γ-rays of energy greater than 0.10 MeV and abundance greater than 1 % are listed.

The Ra-228 activity is a unique function of the age of the Thorotrast since the chemical manufacturing process yields a material which is initially completely free of this isotope. Thereafter the Ra-228 activity, A_1, grows in according to the relation:

$$A_1 = A_o \left[1 - \exp (- 0.6931\ t/\tau_1) \right] \qquad (1)$$

where A_o is the activity of the parent nuclide, Th-232, t is the elapsed time since manufacture, and τ_1 is the half-life of Ra-228. This relationship is illustrated graphically in Fig. 1, from which it may be seen that approximately 50 years must pass before the Ra-228 achieves a constant activity.

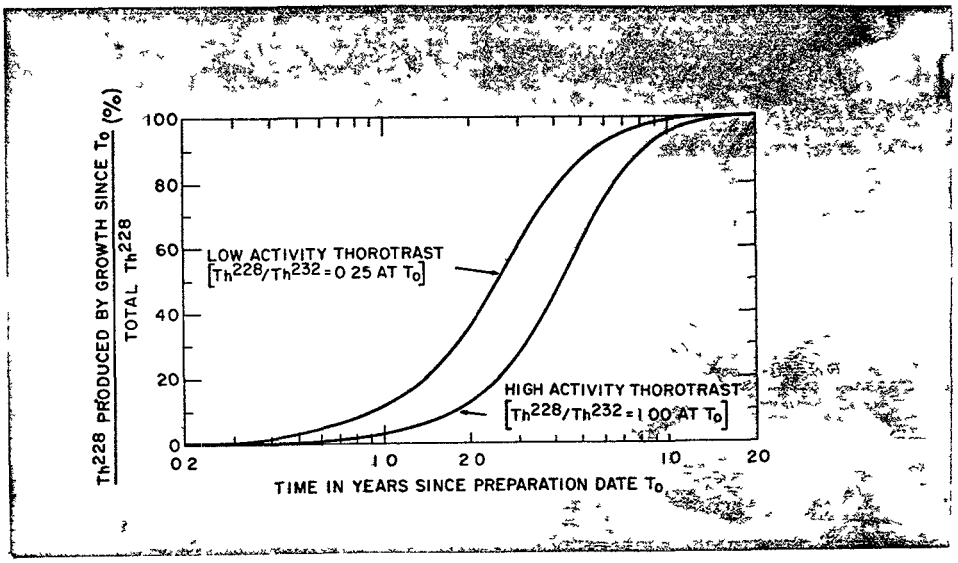

Fig. 1. In vitro activities of Ra-228 and Th-228 in Thorotrast as a function of time since the preparation date. For Th-228, the dependence of the activity on the initial Th-228/Th-232 ratio is shown.

The behaviour of Th-228 is rather more complicated since it is not removed at the time that the Thorotrast is made. Depending on the prior history of the thorium used in its manufacture (and assuming that no Th-228 has been added) the initial value of the Th-228/Th-232 ratio may lie anywhere between zero and unity (in practice, usually between 0.2 and 1.0). At any later time, t, the Th-228 activity, A_2, is given by the equation:

$$A_2 = A_o \left[1 - 1.48 \exp(- 0.693\ t/\tau_1) + 0.48 \exp(-.0693\ t/\tau_2) \right] + A_2^o \exp (- 0.693\ t/\tau_2) \qquad (2)$$

where A_2^o is the initial activity of Th-228, τ_2 is the half-life of Th-228, and the other symbols are as defined above.

The variation of Th-228 activity with time is illustrated in Fig. 1 for several different initial values of the ratio Th-228/Th-232. The uppermost curve applies to the situation where the ratio Th-228/Th-232 is initially unity, as for Thorotrast prepared straight from thorium ore; it reaches its minimum value of about 42 % after an elapsed time of roughly five years. It may therefore be inferred that for all values of the initial Th-228/Th-232 ratio less than 42 %, the thorium had been taken through two or more prior chemical purification cycles. Similarly, for the initial ratio to be less than 25 % there must have been three or more prior purification cycles over a period of not less than about 4 years, and probably much longer.

After an elapsed time of 7 to 10 years from the manufacture of the Thorotrast, its radioactivity, and hence the dose rate associated with it, are no longer very dependent on the initial Th-228 activity that it contained. Since most animal experiments are conducted well within this time interval, the precise activity ratios of Th-232 : Ra-228 : Th-228 in the injection material are important parameters affecting the total dose rate. In the case of human patients with long-term Thorotrast burdens it is not so important to know the radioactive equilibrium status of the injection material, but even in these cases, 10 years is not by any means an insignificant length of time, and uncertainties about the injection material do lead to small but signigicant uncertainties in the estimation of the total cumulative dose.

3. The distribution of activities in Thorotrast

Thorotrast is a colloidal material containing approximately 25 % weight/volume of thorium dioxide (i.e., 25 g ThO_2 in 100 ml Thorotrast), stabilized by the addition of dextrin, and adjusted to a pH of about 8.2 (Wiedemann, this meeting). At least two physical phases can therefore be distinguished - the particles and the solution. In addition it is found experimentally that significant activities are very often adsorbed onto the walls of the glass container, so that this must be defined as a third phase.

At very early times following its manufacture Thorotrast can be visualized as containing only two radioactive species, Th-288 and Th-232, in the ratio of unity or less, and both distributed homogeneously throughout the particulate phase. Thereafter the various daughter activities grow in according to the equations given above, and their distributions throughout the Thorotrast are determined by such parameters as solubility, surface adsobability, and perhaps most important of all, the position of each atom after recoil from the nuclear event which gave rise to it.

3.1. Calculation of recoil ranges in ThO_2

The significance of recoil in determining the position of a radioactive atom in Thorotrast can be demonstrated by considering the case of Ra-228. Here the parent atom Th-232 is located entirely within the particulate phase. Following the emission of a 4.01 MeV α-particle from a Th-232 atom the energy of the recoiling Ra-228 nucleus can be

calculated from the principle of conservation of momentum as:

$$E_r = E_\alpha \frac{M_\alpha}{M_r} = 70 \text{ keV} \qquad (3)$$

where E_α = the energy of the α-particle, M_α = the mass of the α-particle, and M_r = the mass of the recoiling particle. Unfortunately it does not seem to be possible to calculate the range of such an atom in ThO_2 with very great accuracy since no empirical or theoretical equations have yet been developed which can deal adequately with the case where the atomic numbers of the recoiling atoms and of the stopping material are approximately equal. The most accurate equation is probably that derived by Bohr (1948) and modified by Nielson (1956) which quotes the recoil range R_o as:

$$\frac{R_o}{E} = 0.60 \frac{A_1 + A_2}{A_1} \frac{A_2}{Z_2} \frac{(Z_1^{2/3} + Z_2^{2/3})^{1/2}}{Z_1} \qquad (4)$$

where R_o is measured in units of $\mu g/cm^2$, E is the energy of the recoil nucleus in keV, A_1 and A_2 are the mass numbers of the recoil and target nuclei respectively, and Z_1 and Z_2 are their atomic numbers.

It is not obvious how this equation can be applied to stopping materials like thorium dioxide which contain <u>two</u> kinds of atoms. For pure oxygen, R_o/E works out at about 0.073, which is probably a good estimate since $A_1 \gg A_2$ in this case. For pure thorium, R_o/E has the value of 0.227, which is probably an overestimate by approximately a factor of two (Winsberg and Alexander, 1961), since A_2 and A_1 are approximately equal in this case. For ThO_2, assuming that the recoil nucleus loses a fixed amount of energy as it passes each nucleus of a given type of stopping material, it may be shown that R_o/E would have the value $264/(232/0.1135 + 32/0.073) = 0.106$. On this basis the recoil range of a Ra-228 nucleus in ThO_2 works out at approximately 75 Å, and the recoil ranges of the other nuclei in the decay series which are born of α-transitions will be a little longer due to their slightly higher recoil energies (Table 2).

Table 2

Recoil energies of thorium series nuclides

Nucleus	Transition by which it is formed	Recoil energy (Max)
Ra-228	α	70 keV
Ac-228	β, γ	0.1 eV
Th-228	β, γ	16 eV
Ra-224	α	97 keV
Rn-220	α	103 keV
Po-216	α	116 keV
Pb-212	α	128 keV
Bi-212	β, γ	2.3 eV
Po-212	β, γ	19 eV
Tl-208	α	116 keV

If ThO_2 is a microcrystalline material there will in addition be a small proportion of the recoiling atoms which have a very much longer range due to the so-called tunneling effect (Kornelsen et al, 1964).

The important consideration now is whether these ranges are short or long compared to the size of the Thorotrast particles. From measurements on electron micrographs it appears that the particle size is not closely controlled, for it has been variously reported as 30 to 100 Å with a mean of 70 Å (Marinelli, 1964), and 80 to 200 Å (Bensted and Crookall, 1963). Nevertheless these are of the same order of magnitude as the calculated recoil ranges of several of the thorium daughter products and it is therefore to be expected that a substantial proportion of these atoms would escape from the particulate phase of Thorotrast, and thus find their way into the solution. This is likely to make the distribution of activities between the particulate and non-particulate phases very complicated. All the Ra-228 atoms are born within the Thorotrast, and the proportion escaping into the outside solution is likely to remain constant provided that the particle size does not change and that there is no agglomeration of particles. Subsequent daughters in the decay series, however, have several points of origin deriving from the distribution of Ra-228 between the different physical phases. As discussed below, this pattern of distribution, except for Ra-228, is likely to be a function of the age of the Thorotrast. Only those atoms which are born of α-transitions have sufficient recoil energy to escape from the confines of the Thorotrast particles. The recoil energy following a (β, γ) transition is very much lower, but may still be large enough to break chemical bonds. It may be shown (e.g. Evans, 1955) that the maximum recoil energy, E_r, of an atom following β-decay is given by:

$$E_r = 548\ E_\beta\ (1 + 0.975\ E_\beta)/M \quad \text{electron volts}$$

where E_β is the β-particle energy measured in MeV, and M is the mass number of the recoiling atom. Similarly for a γ-transition:

$$E_r = 534\ E_\gamma^2\ /\ M \text{ electron volts.}$$

Thus it may be calculated (Table 2) that Ac-228 and perhaps Bi-212 are the only thorium daughter nuclides which have recoil energies lower than that normally needed for breaking chemical bonds (1 to 5 eV). All the other thorium daughters therefore possess a sufficient recoil energy at least to break the chemical bonds which might be holding them in surface locations on the particles or on the wall of the Thorotrast container - even if the change in chemical state alone were not sufficient to allow them to break free. It is worth pointing out that even when surface adsorption is discounted, a significant fraction of the atoms within the particulate phase of Thorotrast are located on the surface. Assuming for the sake of argument that the particles are spheres of radius 35 Å and that the surface layer has a thickness of 2 Å, then approximately 17 % of the atoms are in surface locations.

The picture that emerges from this analysis is of a material comprising three physical phases: solid particles, solution and surface, and containing two categories of radioactive atoms (1) those with a

high recoil energy born of α-transitions and (2) those of a low recoil energy born of (β, γ) transitions. The effects of recoil are to change the physical phase in which many of the atoms are located. The high energy recoils allow a certain proportion of the atoms to escape into the solution from the particulate phase, and the low energy recoils allow a certain proportion to escape from surface locations on the walls of the container or on the Thorotrast particles themselves. Immediately following their creation, therefore, a substantial proportion of the thorium daughter nuclides are likely to be located within the solution phase. What happens to them will hang upon considerations of solubility and surface adsorbability.

3.2. Solubility and surface adsorbability

The solubilities of extremely small quantities of material in the liquid phase of Thorotrast are not easy to predict, particularly in the case of the thorium series nuclides of which several members may possess more than one oxidation state. The subsequent metabolism of these nuclides of course is determined more by their solubilities in body fluids than in the liquid phase of Thorotrast. Consider for example the case of Th-228 which, in tracer quantities, is soluble at body pH (Stover and Buster, this meeting). Since in Thorotrast the pH is somewhat higher than in the body (8.2 for Thorotrast compared with 7.4 for blood and 6.5 for the Kupfer cells of the liver (Spector, 1956)) it is not unlikely that, in vitro, the soluble Th-228 may precipitate on the surface of the Thorotrast particles or on the walls of the ampoule. However, if the adsorption reaction is reversible, it would be expected that the Th-228 adsorbed on the particles would become solubilized again under in vivo conditions of pH, and it would therefore behave as if it had been soluble in the Thorotrast itself. According to this definition of solubility we can deduce from the biological data compiled by Durbin (1960) and from the recommendations of ICRP (1959) that all the thorium daughter nuclides except Ac-228 and to a lesser extent Pb-212 which are not bound within the particulate phase should behave as if they are soluble.

The loss of activity by adsorption onto the wall of the container rather than onto the surface of the particles is inherently unlikely if the controlling parameter is simply surface area. On the simple assumption that Thorotrast particles are spherical and of diameter 70 Å it can be calculated that each millilitre of Thorotrast presents the enormous surface area of about 2×10^5 cm^2. Nevertheless, appreciable activities are sometimes observed to be adsorbed onto the surface of the container (vide infra). Other variables than just area must therefore be important, of which one is undoubtedly the chemical composition of the glass. It has been reported by Morgan et al. (1964) that the adsorption of radioisotopes onto glass surfaces is primarily a function of their alkali oxide content, and that glasses having a high content of silica adsorb much less than lime glasses. Another important variable is the pH of the solution. The studies reported by Morgan et al. indicate that, in general, adsorption increases as pH increases.

3.3. The age of the Thorotrast

The age of the Thorotrast and the previous history of the thorium used in its manufacture have already been shown to be important variables determining its total radioactivity. They are also important in determining the distribution of active species between the different physical phases. The nuclide which exhibits this effect most markedly is Th-228 which, as we have seen, is initially located entirely within the particulate phase. As time passes these original atoms of Th-228 decay away while new ones are formed through the intermediate steps of Ra-228 and Ac-228. But a substantial proportion of the new Th-228 atoms are either in solution or adhering to a surface. The proportion of "new" Th-228 atoms to the total number of Th-228 atoms varies with time in the manner of Fig. 2, and is dependent on the initial value of the Th-228/Th-232 ratio.

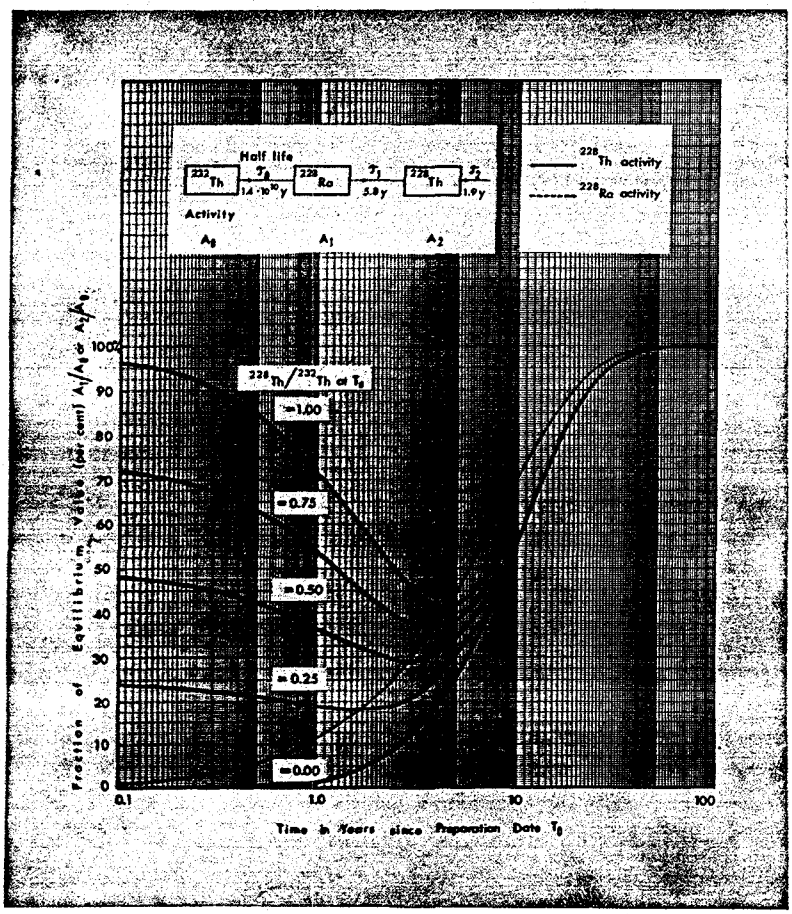

Fig. 2. Proportion of Th-228 in Thorotrast produced in vitro since the date of preparation, relative to the total Th-228 activity.

It is to be expected therefore that Th-228 and subsequent daughters in the decay series will redistribute themselves throughout the Thorotrast in proportions which are continually changing with time until about 10 years from the date of manufacture. At this time the proportion of the total activity outside the particulate phase will have reached a constant minimum. There are important dosimetric implications in these conclusions since the metabolism of Th-228 and other thorium

series nuclides following an injection of Thorotrast is likely to depend strongly on the distribution of activities between the particulate and non-particulate phases. Most of the active species which are soluble will be excreted or at least translocated out of the reticuloendothelial system where the principal deposits of Thorotrast are located. Thus different samples of Thorotrast containing exactly equal activities of Th-228 may give rise to very different dose rates. If, as suggested below, the proportion of soluble Th-228 can rise to as high as 80 % of the total in very old samples of Thorotrast, then as much as 86 % of 80 %, or 69%, might be soluble at the end of the normal 5 year shelf-life period of this material (see Fig. 2, upper curve). Therefore, in vivo dose rates to the RES from Th-228 and subsequent daughters in the series per microcurie of Th-228 injected may differ by as much as a factor of three between very young Thorotrast (containing no soluble Th-228) and 5 year old Thorotrast (containing as much as 69 % of the Th-228 in a soluble form).

4. Experimental evidence on distribution of activities

4.1. Dialysis experiments

One of the most direct ways for studying the distribution of activities between the different phases of Thorotrast is to separate the soluble ions from the particulate phase by dialysis. The only experiment which appears to have been conducted along these lines was reported by Hursh et al (1957). Dialyzing 1 ml of Thorotrast against 500 ml of acidified water (pH 5.0) they found that approximately 98 % of the Ra-224 appeared to be readily diffusible compared with only 30 % of the Ra-228. Neither of the two thorium isotopes was observed outside the dialysis cell.

The greater diffusibility of Ra-224 than Ra-228 is consistent with the theory advanced above that since the process of radioactive decay from Ra-228 to Ra-224 involves a second high energy recoil event, the Ra-224 has an extra opportunity to escape from the confines of the Thorotrast particles. The non-diffusibility of Th-228 is somewhat surprising since it indicates that all the atoms of this nuclide were either bound within or on the surface of the particulate phase. This is not in accord with other experiments reported below.

4.2. Measurements of the activities of Thorotrast solutions and Thorotrast vials

These measurements say nothing about the distribution of activity between the particulate and soluble phases of Thorotrast, but they do give information on adsorption onto the walls of the Thorotrast ampoules. Insofar as this can drastically reduce the total activities of the daughter nuclides as they are actually administered to a patient or animal from the ampoule, they have an important bearing on the dosimetry.

The proportion of activity that is bound in this way is not constant from one sample to another, and indeed it has been found that in some cases no adsorption whatsoever takes place (Rotblat and Ward, 1956). Usually when adsorption losses of this kind do occur the nuclide affected most markedly is Ra-228. But this does not necessarily imply that "soluble Ra" has a greater propensity for adsorption than "soluble Th" since the proportion of soluble Th-228 to total Th-228 is likely to be smaller unless the Thorotrast is very old.

Miller and Marinelli (1958) have reported on one ampoule of Thorotrast containing Ra-228 and Th-228 approximately in equilibrium in which about 50 % of the Ra-228 activity was bound to the ampoule compared to only 17 % of the Th-228. Rundo (1956) observed that the γ-ray activity of one of his empty Thorotrast bottles decayed with the half-life of Ra-228 without showing any increase, thus implying that Ra-228 and Th-228 were in equilibrium. But the original value of the Ra-228/Th-228 ratio in the unopened ampoule was not stated. Autoradiographic measurements by Rotblat and Ward (1956) have also confirmed that appreciable radioactivity may be bound to the glass, but their technique did not permit the relative amounts of Ra-228 and Th-228 to be estimated.

Measurements of the activity ratios in samples of Thorotrast soon after removal from their ampoules have also very often indicated a loss of activity by adsorption onto the walls of the ampoule. Quite commonly the observed Ra-228/Th-232 and Th-228/Th-232 ratios in the sample analyzed have been found too low to be consistent with the known age of the Thorotrast (Hursh et al., 1957; Rundo, 1958; Dudley, 1965).

Some examples of the activity ratios measured in samples of Thorotrast immediately following removal from their ampoules are listed in Table 3.

Table 3

Radioactive equilibrium status of thorium series nuclides in samples of Thorotrast removed from their ampoules [a].

Reference	Sample Code	Th-232	Ra-228	Ac-228	Th-228	Ra-224	Pb-212	Bi-212
Hursh (1965)	AV	100	38	?	33	23	28	?
	H	100	15	?	30	20	28	?
Parr (unpubl.)	062 [b]	100	35.6	35.0	39.1	39.6	37.8	37.3

(a) Numbers are activities relative to Th-232 as 100.0
(b) Estimated standard deviations of these figures are ~ ± 0.5

Nothing can be said from these figures about adsorption losses of Ra-228 since estimates are not available for the Ra-228/Th-232 ratio in the total ampoule. However, the figures do say something about the losses

of thorium daughters further down in the series than Th-228 since these would be expected to be in equilibrium with Th-228 in the ampoule. Hursh's results indicate a significant adsorption of both Ra-224 and Pb-212, the former nuclide being bound in greater proportion than the latter. The results of Parr lend support to the theory that Thorotrast is never consistent in its behaviour since very little adsorption loss of either Ra-224 or Pb-212 (or for that matter of Ac-228 or Bi-212) appeared to have occurred.

4.3. Animal experiments

In the case of a material like Thorotrast a living animal has many of the properties of a dialysis cell. It retains injected particulate material within the reticuloendothelial system (RES) and metabolizes the soluble radioactive ions in ways which are fairly well understood. (In the case of the members of the thorium decay series, all except Th and Ac are largely excreted within a few days or weeks if their half lives are adequately long.) Thus a comparison of the activity ratios observed in tissues containing Thorotrast with the corresponding ratios in the injection material can tell a great deal about the distribution of that activity between the soluble and insoluble phases. The liver in particular is a suitable organ for study since it is the part of the RES which contains the major part of the activity of the whole body, and therefore the interpretation of the results is not so likely to be made difficult by the problem of translocation of activities from other organs. The results must be treated with a little caution however since Thorotrast particles tend to form into aggregates within the RES, and thus the escape of soluble decay products into the general circulation is likely to be impeded (Faber, 1962). Since this effect becomes more and more pronounced as time proceeds, short term experiments of a few weeks' duration are more relevant in the present context than measurements pertaining to Thorotrast burdens of many years standing.

Ra-228:

Perhaps the most significant finding from all these experiments is that a large fraction of the injected Ra-228 is retained by the body (Hursh et al, 1957; Miller and Marinelli, 1958; Hursh, 1965; Parr, 1964; Parr, unpublished) rather than being excreted in the way expected of soluble radium. Therefore it is inferred that this activity is physically trapped inside the Thorotrast particles.

The fractional retention of injected Ra-228 in the body is found to vary from one sample of Thorotrast to another, as might be expected from the known variability in the fractional retention of radium within the ampoule. Unless the amount sticking in the ampoule is known, it is impossible to deduce from these experiments the proportion of Ra-228 atoms in vitro which are able to escape from the Thorotrast particles. In the absence of this knowledge the measured in vivo retention of Ra-228 is merely an upper limit on the probability that a Ra-228 atom does not possess sufficient recoil energy to escape from a Thorotrast particle in vitro.

Some miscellaneous analyses of rat, dog and human livers one or more weeks after administration of Thorotrast are presented in Table 4. The Ra-228 figures can be taken to indicate that the fractional retention of Ra-228 atoms within the Thorotrast particles in vitro was of the order of 20 % or less. In fact the figure of 20 % is probably fairly well established in this case since the Thorotrast used in this experiment (batch number 13098) was from the same batch as sample 62 in Table 3, and the latter did not show much evidence of a deficiency of radium (as Ra-224). The measurements of Miller and Marinelli (1958) also lead to a similar conclusion if their figure of 50 % loss of Ra-228 in the ampoule is taken into consideration. The fractional retention of Ra-228 atoms within the Thorotrast particles in vitro works out at 18.5 % in that case.

These measurements relate to the Ra-228 contained within the Thorotrast injection. Other measurements throw some light on the fate of the Ra-228 atoms which are born within the body after administration of the Thorotrast. Excretion data reported by Hursh (1965) (average of about 0.5 % of the total body burden of Ra-228 excreted per day during the first 100 days after Thorotrast administration) suggest that only about 6 % was in a non-dialyzable form. This seems rather low in view of the estimate of 20 % obtained above. At much later times (reviewed by Kaul at this meeting) the measured Ra-228/Th-232 ratios in small liver samples suggest that ~ 40 - 65 % of the radium atoms are retained within the Thorotrast particles, but at these late times the particles are formed into aggregates so that escape of Ra-228 atoms is probably impeded.

Ac-228:

Unfortunately, the liver has a high affinity for actinium so that it is not likely to act as a very efficient dialysis cell. Therefore the metabolism of Ac-228 does not provide any useful information about its distribution in vitro. The data on recoil energies suggest that it is likely to be distributed in much the same way as its parent Ra-228.

Th-228:

Since ionic thorium is taken up by the skeleton rather than the RES (Stover and Buster, this meeting), the liver probably functions quite well as a dialysis cell for this element. The data in Table 4 suggest that as much as 50 % of the Th-228 in a Thorotrast sample can be found outside the particulate phase. This is not surprising in view of the fact that its "grandparent" Ra-228 is also largely located outside the particles. The main significance of these measurements is in showing that Th-228 can exist in Thorotrast in a fairly soluble form - either in true ionic solution or loosely bound to the surface of the Thorotrast particles. It should be emphasized again that the proportion of soluble Th-228 would be expected to vary with the age of the Thorotrast, and if the estimate made above is correct that 80 % of the Ra-228 atoms are located outside the particulate phase, the proportion of soluble Th-228 could rise to 80 % in very old samples of Thorotrast.

Table 4

Calculated steady-state activity ratios of thorium series nuclides in liver of rat, dog and man.

Reference	Animal code number	Thorotrast batch number	Duration of burden (days)	$\frac{\text{Ra-228}}{\text{Th-232}}$	$\frac{\text{Ac-228}}{\text{Ra-228}}$	$\frac{\text{Th-228}}{\text{Ra-228}}$	$\frac{\text{Ra-224}}{\text{Th-228}}$	$\frac{\text{Pb-212}}{\text{Ra-224}}$	$\frac{\text{Bi-212}}{\text{Pb-212}}$
Parr (unpublished)	67 (rat)	13098	41	0.19	0.98	0.86	0.38	0.37	0.37
	78 (dog)		21	0.18	0.96	0.87	0.55	0.34	?
	83 (man)		26	0.20	?	0.88	0.53	?	?
	85 (man)		48	0.19	?	0.88	0.59	0.63	?
Parr (unpublished)	72 (rat)	09940	35	0.34	0.87	0.65	0.54	0.65	0.72
	73 (rat)		38	0.38	0.99	0.77	0.51	0.63	0.88
Miller and Marinelli, 1958	- (man)	07860	9	0.37 (0.19)[a]	?	0.57 (0.48)[a]	?	?	?

a - Calculated by reference to the total activity in the ampoule, as distinct from the total activity in the injection material.

Because of their low recoil energies (maximum 16 eV), those Th-228 atoms which are born within the particulate phase have an insignificantly small chance of escaping into the outside solution unless they happen to be located within the surface layer. It may perhaps be this mechanism of excape which can explain the 10 % loss of Th-228 relative to Ra-228 observed in the long term Thorotrast patients reviewed at this meeting by Kaul.

Ra-224, Pb-212, Bi-212:

The metabolic data on these elements (e.g. Table 4) provide a direct insight into their fractional retentions relative to the total activity generated within the particles. This, of course, is not the same as the total in vitro activity because as much as 80 % of the Th-228 from which these nuclides are derived may be located outside the particulate phase.

The metabolic data are not entirely in accord with what might be expected from the calculations on recoil energies (Table 2). For example, the retention of Ra-224 relative to "bound Th-228" (40 - 60 %) would be expected to be smaller than the retention of Ra-228 relative to Th-232 (20 %). Likewise, Bi-212 would be expected to have a very large retention relative to Pb-212 since its recoil energy is only 2.3 eV, an amount certainly insufficient to allow it to escape from within the Thorotrast particles. This latter discrepancy can probably be explained by the fact that the liver is not acting efficiently as a dialysis cell for Pb-212 (biological half-life is 1947 days, ICRP, 1959) and therefore many of the Pb-212 atoms retained in the liver are not actually bound within the Thorotrast particles.

Rn-220:

From thoron breath analyses of Thorotrast patients and calculations involving the circulation time of the blood, it is possible to make a rough estimate of the proportion of thoron atoms generated within the Thorotrast deposits which escape into the general circulation. Hursh (1965) arrived at the figure of 16 %, and Grillmayer et al. (1964a) concluded that it might even be as high as 20 %. However, the metabolic data contained in Table 4 suggest that even 20 % may be an underestimate. Because of the long biological half-life of Pb-212 in the RES, the apparent washout of Pb-212 relative to its "great-grandparent" Ra-224 is probably due more to washout of Rn-220, one of the intermediate decay products, than to washout of Pb-212 itself. On this basis the in vitro escape of thoron from the particulate phase of Thorotrast into the solution is likely to be at least as high as 35 - 65 %.

5. Summary

A considerable amount of experimental work remains to be done before we can claim to have a very detailed understanding of the mechanisms which determine the distribution of thorium daughter activities among the different physical phases of Thorotrast. For this reason, some of the conclusions which are incorporated into the following summary are not very firmly established. In particular the estimates of fractional retentions in the particulate phase are probably only very approximate, and significant differences between one batch and another would not be unexpected.

(1) The total in vitro activity of Thorotrast varies significantly with time - but in an accurately predictable manner - until about 50 years from the date of manufacture. The initial Th-228/Th-232 ratio has an important determining effect on the total activity during approximately the first 7 to 10 years.

(2) At least three physical phases can be distinguished in Thorotrast: the particles, the solution, and the walls of the container. A possible fourth phase is the surface of the particles.

(3) The escape of activities in vitro from the particulate phase of Thorotrast is probably due to high-energy recoils. The calculated recoil ranges for thorium daughters which are born by α-transitions are of the same order of magnitude as the size of the particles. A second possible mechanism of escape for atoms located on the surface of the particles is by low-energy recoil following (β, γ) transitions. Both these mechanisms are likely to be strongly influenced by the size of the particles.

(4) Approximately 80 % of the total in vitro activity of Ra-228 (and Ac-228) is located outside the particulate phase. The corresponding ratios for Th-228 and subsequent daughter isotopes are not constant but increase with time reaching their maximum after about 10 years. Significant fractions of the Ra-224, Rn-220, Po-216 and Tl-208 activities which are born within the particulate phase escape into the surrounding medium. Animal experiments suggest that the fractions escaping are not less than about 40 - 60 % for Ra-224, and 35 - 65 % for Rn-220. Variations in the precise pattern of distribution of thorium daughter activities in Thorotrast at the time of administration are likely to affect the subsequent in vivo dosimetry for as long as 10 years.

(5) Significant proportions of the total in vitro activities of Thorotrast are sometimes but not always bound to the walls of the ampoule. Ra-228 appears to be adsorbed more strongly than Th-228. The principal factors which determine adsorption are probably the chemical composition of the glass and the pH of the solution.

FORMATION AND BEHAVIOR OF COLLOIDAL PARTICLES AS A FUNCTION OF PHYSICO-CHEMICAL AND BIOLOGICAL CONDITIONS

J. Lafuma

The nuclear industry uses thorium and other elements of comparable physico-chemical characteristics. These elements, chiefly the rare earths and transuranic elements such as Pu, constitute an important fraction of contamination risks. Their biology has been extensively studied, both in its metabolic aspects to set maximum permissible limits and in its therapeutic aspects to improve treatment of accidentally contaminated persons.

The main characteristic of these elements is their hydrolysis at the pH of living matter. The ion does not exist in free form, nor is there an equilibrium between the ion and its biological carrier, as for example with Ca. These elements are found in vivo in only three structures: (1) ion complexed with a biological carrier, (2) hydroxide, whose degree of polymerization varies according to conditions, and (3) insoluble oxides. These three structures have been studied under various conditions of preparation and administration. This discussion is limited to the biology of radiocolloids, namely polymers of hydroxides.

Radiocolloids of the rare earths and Pu are prepared by neutralization of acid solutions, chiefly nitrates and chlorides. The conditions of neutralization, along with the mass of the element and the valency, determine the particle size and stability of the colloid. Rare earths, such as Ce-144 III, without carrier, hydrolyze at a pH of about 6. Since the biological environment is approximately neutral, the colloid has limited stability and will rapidly degrade. If one uses Ce-144 III, an activation product with considerable stable Ce carrier, the colloid obtained will have a greater particle size and stability. Pu-239 IV, of which one Curie amounts to 16 grams, hydrolyzes at pH 2 and in biological surroundings is very stable. Th IV hydrolyzes at a pH of about 3.5.

When a colloid is injected intravenously it first encounters the pulmonary system. The amount retained in the lungs increases with the particle size. The fraction which is not retained during its first passage through the lungs will be dispersed throughout the body, and will collect in three organs: liver, spleen, bone marrow. The partition apparently is determined essentially by the conditions of circulation through the organs. It is noteworthy that if the spleen is removed before injection, the entire activity which would have been deposited there is instead found in the liver. Two explanations of this observation are possible: an increased circulation to the liver, or the existence of two different ranges of particle size, one of which can be taken up by liver or spleen, the other by bone marrow.

The particles retained in the lung may subsequently be handled in two quite different ways: phagocytosis by the pulmonary cells, or degradation and reintroduction into the blood circulation. Phagocytosis is a rapid phenomenon: intracellular particles may be found a half hour after injection. The cells which thus accumulate radiocolloids are

drained toward the lymphatic ganglions in the trachea-bronchus region. A few of them penetrate the pulmonary epithelium and are found in the alveolar lumen. This mechanism is symmetrical to that observed after inhalation of colloids.

Degradation proceeds by detachment of monomers. These are immediately bound to biological carriers which take them to the organs where they are deposited: liver and bone. No deposition occurs in the spleen when the element is transported in the plasma in monomeric form.

If the radiocolloid is injected into an artery, it will be retained in the capillaries of the organ and subjected to a process of degradation. If it is injected locally into tissue it will never be found in colloidal form in the plasma; instead, it remains in situ and is eliminated only very slowly. A part will be phagocytized and drained by the lymphatic route to the chains of ganglions which act as successive filters. The other part, after degradation and complexing by a biological carrier, will diffuse in the interstitial fluid and then pass via the blood to the liver and bone.

Radiocolloids located in the reticuloendothelial system of the liver are eliminated by a double process: cellular transport through the lymphatic system, or local degradation followed by biliary excretion. Radiocolloids in the marrow or spleen are slowly degraded, forming complexes with organic molecules and being transferred to liver and bone.

The association of rare earths or Pu with organic molecules is quite different from that of the alkaline or alkaline earth elements. Elements like Ca are ionic at pH 7, and their binding to proteins is characterized by the laws of equilibrium: protein-$Ca^{++} \rightleftarrows Ca^{++}$. There always exists in the plasma an ionic fraction. Rare earths and Pu, on the contrary, are always bound to the carrier molecules, be it as ions or hydroxide monomers. Thus bound to the carrier, they are either assimilated with it into the organ or exchanged. In the liver the protein carrier is stopped at the periphery of the cells. The passage of the radioelement into and through the hepatic cell is rapid. Elimination occurs by the biliary route and no reabsorption takes place in the intestine. The biological period of the hepatic system is less than a week for such structures.

In the bone two different biological mechanisms are possible according to whether the organic carrier molecule is directed toward the zone of growth or destruction. In the growth zone assimilation occurs into the bony system and autoradiographs are yielded quite resembling those obtained with Sr-90 or Ca-45, for example. In the region of destruction, bordering the marrow, the radioelement is detached from the carrier molecule, probably by exchange with Ca ions which are present there in high concentration. Hydrolysis and polymerization take place in situ, and one can observe the presence of the radiocolloid at the edge of the marrow. These deposits grow, forming real "hot spots". With Pu, it has been possible by intramuscular injection to obtain radiocolloids localized uniquely in this region. Histochemical analysis shows that these colloids consist not only of Pu but also of Fe, a fact which is not surprising since these elements are related in the periodic system.

This summary view of the biology of radiocolloids gives an understanding of the dosimetric difficulties. A first difficulty is that the stability of the radiocolloid and therefore its resistance to degradation is not constant with time; it progressively increases. It is therefore difficult to know a posteriori what conditions existed at injection. Another difficulty is the complexity of the metabolism of such elements; the liver and spleen burdens have a tendency to decrease with time, while the skeletal burden increases. A last difficulty is the creation of "hot spots", even if initially the radioelement is completely dispersed. With Pu, an α-emitter, one sees already by the end of a month cellular lesions at the periphery of the bone marrow for burdens which, if uniformly dispersed in the bone, would correspond to about 100 pCi/g. These cellular lesions, which lead to the death of the cells that have phagocytized the radiocolloid, prevent its elimination and accentuate the process of local polymerization - therefore the importance of this process for "hot spot" formation.

In conclusion, even if the data furnished by human cases permit the establishment of a relation between quantity injected and lesion produced, metabolic studies show the importance of the conditions of contamination for the subsequent fate of the radioelements. While alkaline and alkaline-earth elements have the same biology, whether entering the body orally or by injection, the rare earths and transuranic elements have an infinity of metabolisms, rendering extremely difficult the establishment of maximum permissible limits.

SEQUESTRATION, AGGLOMERATION AND REDISTRIBUTION OF ThO_2 COLLOIDAL PARTICLES IN BLOOD AND TISSUE

M. Faber and T. Mueller

1. Introduction

It is characteristic for Thorotrast when injected into animal or man that this chemically inactive dioxide will be deposited in the tissues and will stay there for the rest of the life of the host. Attempts have been made to demonstrate that Thorotrast might be excreted, but apart from minimal losses just after the injection these experiments have only shown that it is possible to withdraw parts of the daughter products from the organism.

Thorotrast has been used under very different conditions. In some cases the solution has been deposited outside the vascular stream more or less inadvertently. The Thorotrast will then be contained within the tissues and as far as it is known it will stay there perpetually except in some cases where gravity will tend to produce a migration. If Thorotrast is brought into the cavities of the organism there is a rapid flocculation and precipitation of the thorium dioxide granules as has been studied for the kidney pelvis by Puhl (1932), for peritoneum by Paillif (1953) and for pleura by Schwaiger (1950). They all describe how the flocculated Thorotrast is taken up by macrophages and deposited first of all in the sub-endothelial connective tissue. After injection into the pleura Schwaiger also notes an uptake into the Kupffer cells of the liver. In these cases of direct extravascular deposition there appears to be a tendency for the Thorotrast to retain the daughter products as was shown by Rondo (1957) for the neck deposits. This will of course give rise to a number of special problems some of which may be dealt with later on.

More important are the problems of what happens if Thorotrast is injected intravenously. After intravenous injection Thorotrast is distributed with the blood stream to be taken up by the phagocytes of the reticuloendothelial system wherever they are present in the organism. We know furthermore that it is redistributed after this primary phagocytosis, and with time we know that certain changes take place which result in storing the Thorotrast in connective tissue.

This evolution can probably best be described in three stages. The first stage is the time from injection until the primary phagocytosis is completed. The second stage should then be from the completion of primary phagocytosis until the end of the primary rearrangement. In the third stage occur the later shifts in localization of Thorotrast.

2. First stage

The knowledge of the handling of Thorotrast after intravenous injection is surprisingly inadequate. The pharmaceutical evaluation of Thorotrast in 1930-40 was mostly centered on the uptake in the liver and less on the processes necessary before phagocytosis can take place. Even

the knowledge of the mechanism of phagocytosis in the body is relatively scant and is, as far as Thorotrast is concerned, mainly occupied with wishes of getting a blocking of the reticuloendothelial system. During recent years we have seen an increasing realisation that a pretreatment of a colloid can be a prerequisite for phagocytosis. This has been most clearly described by Kniseley (1948).

This led us into a study of what happened when Thorotrast was injected intravenously into rabbits. To get a sufficiently high concentration of Thorotrast in the blood stream to permit quantitative measurements without too large blood samples, we had to use relatively large doses. All the rabbits have been injected with 12 ml unless otherwise stated. We shall start by describing the changes in concentration of Thorotrast in the blood stream. After injection we find in repeated experiments that Thorotrast does not behave like other colloids in that its concentration does not follow the expected immediate exponential decrease. The thorium concentration shows only a very small fall in concentration up to 1.5 or 2 hours. After this delay there appears a sudden change in the rate of disappearance and an exponential decrease in the concentration of Thorotrast sets in with a halflife of 1.5 - 2 hours. It was furthermore found that the duration of the delay was dose-dependent. Injection of smaller doses gave a shorter delay before phagocytosis.

The result was not quite unexpected as previous studies in this laboratory could indicate such a behaviour. This result could be due to different effects. We first studied whether the large amount of Thorotrast could give rise to a blocking of the reticuloendothelial system. In order to test this question we injected Thorotrast in the normal amount simultaneously with colloidal radioactive gold. We could then measure the time of disappearance of the colloidal gold by measuring Au-198 in the blood. The results were quite unambiguous. The colloidal gold had a halflife of 1.5 min when injected alone and rose only to 4 min when Thorotrast or dextrin alone was injected. We did not see changes in the disappearance rate of the colloidal gold which could be compared to the plateau seen in Thorotrast. Experiments using heat-denatured rabbit albumin with particle sizes 5 to 20 times as large as Thorotrast showed identical results.

These results indicated to us that the phagocytosis of Thorotrast had to be preceded by certain chemical or physical changes. As described by Dr. Wiedemann, Thorotrast is a colloid of thorium dioxide with dextrin as stabilizing agent. We therefore thought that the dextrin might be of significance to this delay in phagocytosis. From the point of view that dextrin might be split from the thorium dioxide we studied the halflife of dextrin in serum. We found to our surprise that it did not correspond to the one found for the thorium dioxide. The dextrin showed an initial decrease which is exponential and reached 15 % in less than 10 minutes. It is now possible to demonstrate the presence of a large amount of dextrin in liver homogenates evaluated in relation to the amount of thorium dioxide present. Although most of the dextrin appears to be immediately taken up by the reticuloendothelial system, a certain part remains in the blood stream for another couple of hours. During the initial disappearance of dextrin the rabbits show an increase in blood sugar concentration probably due to enzymatic splitting of dextrin in the blood. We are now left with a thorium dioxide preparation circulating in the blood with a small amount

of dextrin which we are so far unable to describe further, whether it is free or present as a regular coating of the particles.

When the protecting dextrin has disappeared the colloidal thorium dioxide changes in physical-chemical capabilities; it will now as a hydrophobic colloid precipitate protein or be bound to serum proteins. We have tried to determine whether such a binding takes place and as mentioned we had in mind the experiments performed by Kniseley (1948). They indicated that the fibrinogen-fibrin reaction is of some importance for the preparing of heparin. This point of view was to some extent supported by earlier experiments in this laboratory which tended to show that the fibrinogen concentration of blood serum decreased after Thorotrast injection. It was also supported by the histological finding of fibrinlike threads in the cells where the thorium dioxide has been taken up (Johansen, 1952). We have, however, not been able to detect the first-mentioned effect. Furthermore, heparin is without influence on Thorotrast phagocytosis, and we have not been able to prepare a thorium-heparin-fibrinogen complex. By gel-filtration through Sephadex we have been able to demonstrate the presence of a high molecular protein in the same fraction as Thorotrast, but only in plasma samples taken in the presence of heparin. We do not know which protein is present and we have no knowledge of the state of binding between the Thorotrast and the protein. The molecular weight of the protein is above 200,000, which does not exclude fibrinogen, but we must also take the macroglobulins into consideration as they are known to be active in metal-binding of other types. The technical problems involved in this study are considerable due to the presence of the Thorotrast particles. The size of the particles will not permit the use of the normal supporting media for gel-filtration, electrophoresis etc.

These experiments have all been performed with rabbits, but a paper by Ekholm et al. (1964) demonstrated by very simple means that the same delay in the disappearance of Thorotrast is found in cats. Whether the same mechanism holds true for other animals or for man is so far unknown, partly due to the dose effect. The experiments published on the disappearance of Thorotrast from the blood of mice and dogs show a rapid decrease from the time of injection and no initial horizontal part, but the dose in these experiments was very small.

In an interesting series of experiments Rowley (1963) has demonstrated Mast cell damage after injection of Thorotrast, and demonstrated that this Mast cell damage probably is due to the dextrin content. We have been able to persuade Mr. Horn to make a couple of histamine measurements on blood from Thorotrast injected rabbits. In both experiments a decrease in the histamine content was demonstrated, which does not support the point of view that Mast cell damage should be of major significance in the primary handling of Thorotrast. However, these results are of course very preliminary.

It must be clear from the preceding that our studies do not yet permit us to give a full description of what happens when the Thorotrast particles are circulating in the blood just after the injection. Any conclusions as to what may be the state of the particles if they are released into the blood after a previous phagocytosis are of course not possible.

3. Second stage

When the thorium dioxide is cleared from the blood stream we enter the second stage. We know from numerous histological studies that the particles are taken up by macrophages and other phagocytic cells primarily in liver and spleen, but bone marrow, adrenals and lung as well may be active. Even with small doses deposits may be found on the endothelial surface of capillaries in many organs and when larger doses are used some endothelial surfaces may be completely covered by Thorotrast. This is for instance the case of the glomerulus, where in rabbits injected with doses of 100 ml we have seen the whole structure covered by Thorotrast.

If we restrict ourselves to smaller doses and look primarily at liver and spleen we find slightly different pictures. In the spleen, part of the granules are immediately taken up in macrophages, but a not insignificant part may be found free in the reticulum. After some weeks, however, all the granules are found intracellularly, and these cells tend to form multinuclear giant cells.

The liver is more interesting due to the lower uptake of Thorotrast per unit weight. This permits us to see a more precise picture. In the first days after injection Thorotrast-laden macrophages are seen fairly evenly distributed in the liver lobules. If we look at the rabbit we will see that the particles shift, and after some time, from 2 - 6 months later, we find a steadily increasing part of the granules located in the portal spaces. The significance and mechanism of this shift in location is only partly understood.

After the primary uptake it is quite evident, as already shown by Irwin (1932a, 1932b), that part of the macrophages move into the vascular system and are transported to the lung by the blood stream to be caught here. The cells may be dead or may die in the lung. At any rate, after some months when these cells are getting rarer, the lung contains Thorotrast granules mostly in leucocytes, and there is a tendency for the lung to be practically free after a further period.

The duration of this cellular Thorotrast transport is not too well known in rabbits, and is of course still more difficult to evaluate in man. We have, however, seen Thorotrast-filled macrophages free in the vessels of the spleen in a case where the spleen was removed close to 20 years after the injection of Thorotrast.

This interesting transport mechanism is not restricted to Thorotrast. Patek and Bernick (1960) and Frankel et al. (1962) have shown that as far as the cellular behaviour and as far as the time schedules are concerned in small experimental animals, there is no difference between Thorotrast and the non-radioactive carbon of India ink.

During these first months there is a marked change in the size of the particles inside the macrophages. Instead of a homogenous population of small granules visible in the microscope we now find large granules growing. The increase in size has been beautifully described by Guimaraes and Lamerton (1956). The basis for this aggregation is unknown. It seems

probable, however, that the aggregation is delayed or damaged in animals injected with specially-prepared Thorotrast having an elevated α-ray emission rate. If this is the case, some cellular mechanism might be involved.

The radiological results of such a regrouping are difficult to evaluate quantitatively, but it must be admitted that the possibility for a wash-out of daughter products is as good as it can be, and we hope to be able to demonstrate this by direct measurements.

4. Third stage

There is reason to believe that even while this redistribution is taking place, at least some of the Thorotrast enters the third stage and goes to more permanent deposits. The depositions around the portal vein must be considered such a place, and the deposits here tend to enclose themselves in a certain but not imposing amount of connective tissue. In addition, there is a movement in the liver towards the capsule where we find relatively large amounts of thorium. There can be no doubt, however, that any change in the structure of the liver which gives rise to necrosis will catch the Thorotrast. If it is then followed by connective tissue proliferation, the Thorotrast will be locked up for the lifespan of the organism. A clinical finding which supports this is the peculiar netlike structure seen in the X-ray picture of Möbius (1964) from a case of hepatic cirrhosis previously injected with Thorotrast. Such a picture has not, I believe, been seen in non-cirrhotic patients.

That this is so can also be demonstrated in animal experiments. I mentioned the rabbits injected with Thorotrast enriched in α-ray emitters. Two of these have died and show identical liver changes. Macroscopically there is a small liver with nodules on the surface, and histologically a classical cirrhosis but without any Thorotrast in the liver tissue itself. All the Thorotrast is concentrated in narrow bands of necrotic tissue with the beginnings of connective tissue proliferation.

What are the radiological consequences of such a deposition? It is so far not possible to give a definite statement, but the parallelism to the neck deposits is evident, and here it has been measured that there is no wash-out of daughters. It may therefore be expected that the same is the case in a fibrotic tissue like the one mentioned.

Quite another question is how this lack of wash-out can be explained. The first suggestion has been the low degree of vascular supply to such tissue. This would be acceptable if only the short-lived daughters were the ones captured in the sclerotic tissue. This is, however, not the case. No daughters are released, and to suggest that bad vascularity could retain a daughter product with a halflife 5.7 years (Ra-228) appears to me to be unacceptable.

If we search for another mechanism there appears to be one which merits more consideration. One of the classical findings in sclerotic connective tissue, and very evident in Thorotrast-containing tissues, is the calcification which is increasing with time. That Thorotrast may be of significance

in the induction of calcification has been shown by Selye (1962) in his studies on calciphylaxis. If we accept that connective tissue containing Thorotrast will calcify, we also point to an easily acceptable explanation for the lack of wash-out. The steady deposition of calcium should pick up whatever traces of radium are released by the decay of thorium and hold it inside the sclerotic tissue. If such a mechanism could be verified some of the peculiarities of Thorotrast would be better understood.

What is the evidence that such a final deposition may be of influence on the wash-out of daughters and thereby on the radiation dose from Thorotrast. I have mentioned the neck deposits. I have tried to calculate an index between thoron in breath and activity of liver (Faber, 1962). This index showed the expected decrease with time. Other factors may, however, be active to give this result. If the thoron in breath is dependent on the amount of thorium in the lungs, which appears reasonable, and if the thorium content of the lung is decreasing with time, this may invalidate the index.

Until further studies are available the mechanism must rest on the not very quantitative histological evidence.

ELECTRON MICROSCOPE OBSERVATIONS ON THOROTRAST IN RAT LIVER*

G. Grampa

Due to its high electron density Thorotrast is easily recognizable in animal tissues and cells by electron microscopy, and for this reason it has been used as a tool in the study of phagocytosis by several investigators (Hampton, 1965; Sampaio, 1956; Wiener et al., 1964). Electron microscopy also provides data of interest in regard to the biological absorption of Thorotrast and to related experimental and human pathology.

I wish to present in this panel some observations made during an investigation on Thorotrast distribution in the rat liver:

(1) Thorotrast particles are remarkably uniform, measuring approximately 70 Å in diameter. Aggregates of larger size are made up by masses of elementary particles.

(2) Thorotrast is phagocytized very rapidly by Kupffer cells. Particles are seen in small invaginations of the cell membrane and in cytoplasmic vacuoles 5 minutes after injection of 1ml of Thorotrast in the femoral vein. Cellular uptake has been observed as early as one minute after Thorotrast injection.

(3) Later on, Thorotrast deposits in cytoplasmic vacuoles become larger and denser, obscuring cellular details.

(4) Focal cytoplasmic degenerations, in the form of whorls of membranes, swelling of mitochondria and multivesicular bodies are a common finding. Thorotrast particles are sometimes observed within mitochondria.

(5) Hepatic parenchymal cells do definitely absorb Thorotrast, even if to a much lesser extent than Kupffer cells. Thorotrast is usually seen in peribiliary bodies close to the bile canaliculus. This electron microscope observation may be of importance with reference to the occurrence of epithelial tumors of the liver in animals and in humans injected with Thorotrast.

(6) Electron microscope study of Thorotrast induced pathology should be exploited. Apparently, no human case has yet been examined at the ultrastructural level.

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* The author conducted this study at the Dept. of Pathology, Downstate Medical Center, S.U.N.Y., Brooklyn, N.Y., while a recipient of a NATO grant. The help and criticism of Dr. Lawrence Herman and Dr. Patrick J. Fitzgerald are highly appreciated.

DOSE IN LIVER AND SPLEEN AFTER INJECTION OF THOROTRAST INTO BLOOD

A. Kaul

The estimation of the radiation dose-rates in the liver and spleen of persons after injection of Thorotrast into the blood presumes a knowledge of a series of parameters which are here discussed in detail:

(1) Distribution of Th-232 and its daughters within the organism

(2) Excretion of Th-232 and its decay products from the body

(3) Steady-state activity ratios between the members of the thorium decay chain within the deposits

Moreover, the calculation of the cumulative radiation dose in the deposits presupposes a knowledge of or assumptions on the distribution of the ThO_2 aggregates and the daughters of Th-232 within the organs throughout the duration of the Thorotrast burden.

1. Distribution of Th-232 and its daughters within the organism

1.1. Analysis of autopsy and biopsy material

From the early period of the use of Thorotrast as an X-ray contrast medium it has been known that the ThO_2 particles are deposited in the reticuloendothelial system (RES) within a few hours after the injection into the blood and are retained in the RES thereafter. Preferential uptake is in the liver and spleen. However, up to some years ago the problem of the distribution of Thorotrast within the RES remained open.

Assuming the total amount of Thorotrast to be deposited within the organs of the RES proportional to the mass of the organs, the Thorotrast content of the liver and spleen would be in the ratio 92 %/8 % (mass of the liver of the "standard man" = 1700 g, mass of the spleen = 150 g). The distribution to the organs liver, spleen and the red bone-marrow (standard mass = 1500 g) would be 51 % : 5 % : 44 %. However, radiographs suggest a greater concentration in spleen than liver (even after allowance for spleen shrinkage which in long-term cases may reduce this organ to half of its normal size).

Direct measurement of the distribution of Th-232 and its daughters between liver and spleen became possible in some cases while measuring the total body content of Thorotrast patients in vivo before and after extirpation of the spleen, or by the analysis of tissue samples obtained at autopsy. The results of these investigations showed about 75 % of the total Ra-228 and Th-228 activity of the liver and spleen to be located in the liver and 25 % to be deposited in the spleen (Kaul and Rajewsky, 1965). Similar results for Th-232 were obtained

from the analysis of tissue samples with an α-coincidence method (Stahlhofen, 1964b). Comparable results from external γ-ray measurements were published by Rundo (1957); the corresponding values were 79 % and 21 %, respectively. These results confirm the radiological evidence of a higher specific thorium content of the spleen which proved to be about 6.5 times that of the liver (Kaul and Rajewsky, 1965). Further investigations have revealed that about 30 % of the total amount of Thorotrast injected into blood is deposited in the skeleton and bone marrow, as discussed in a subsequent paper at this meeting.

1.2. Analysis of body burden of Th-232 daughter products by whole-body counting

Investigations of both the amount and distribution of Th-232 daughters within the bodies of Thorotrast patients were carried out with the Frankfurt total-body γ-ray spectrometer. The device, consisting of a non-collimated 8" x 4" NaI(Tl) crystal in a steel room, has been described earlier (Kaul and Rajewsky, 1965). By movement of the detector in steps along the axis of the patient lying on a stretcher, the distribution pattern of the incorporated Thorotrast could be determined even with an uncollimated crystal. With the aid of a collimating device similar measurements have been done by the IAEA (Dudley, 1964). To calibrate the spectrometer, distribution patterns similar to those observed in vivo were imitated in a phantom.

The results of these analyses of different distribution patterns of incorporated Thorotrast by whole-body counting have been published elsewhere (Kaul, 1964). In cases where the predominant deposits of colloidal ThO_2 are in the liver and spleen, a quantitative determination of the body burden of Th-232 daughters is rather simple by comparison of the normalized in vivo and phantom distribution curves. The analysis of more complicated distribution patterns, such as simultaneous perivascular deposits, is much more difficult. Useful results can nevertheless be obtained. In a series of cases the analysis of whole-body measurements before and after extirpation of the spleen or of a perivascular deposit led to the same results within 10 to 15 % as did the subsequent examination of the biopsy material and samples of tissue obtained at operation or autopsy on the same cases.

2. Excretion of Th-232 and its daughter products

2.1. Excretion of Th-232

The first quantitative results on the elimination of Th-232 from the bodies of Thorotrast patients were published by Hursh et al. (1957). The daily excretion of Th-232, Ra-228 and Ra-224 was studied in two cases, one as long as 108 days after the injection. The results indicated that the patients excreted Th-232 at an average rate of 0.0004 to 0.0007 % of the dose per day, corresponding to a biological half-life of 420 - 760 years. With the exception of an initial unexplained high value for the urine of one patient on the first day the fecal excretion rate was higher than the urinary excretion by a factor of 10 to 100. It is clear that the amount of thorium element excreted after Thorotrast administration is negligible.

2.2. Excretion of Ra-228

The results of Hursh et al. (1957) on Ra-228 indicated that the patients excreted Ra-228 with the faeces and urine at an average rate of 0.026 % of the body burden per day. Though these values were not well established in the authors' opinion, our own investigations (Kaul and Rajewsky, 1965; Kaul, 1964) yielded a similar result of 0.03 %/day. Furthermore, Grillmaier (1964) obtained for 50 cases an average value of 0.034 %/day. The value of 0.03 % of Ra-228 body content excreted per day means that if little Ra-228 is initially injected the body Ra-228 content increases during the years to a steady-state value equal to about 50 % of the Th-232 activity, in agreement with the results by analysis of autopsy and biopsy material (see section 3.2. and section 3.3.).

2.3. Excretion of Ra-224

The investigations by Hursh et al. (1957) proved that Ra-224 is excreted at an approximately constant rate of 2.6 % of the body burden per day, beginning at about 50 days after the incorporation of Thorotrast. In addition, the authors observed that the major route of excretion is the faeces, the urinary excretion rate being less than one tenth as great. These results were confirmed by Kuth and Oberhausen (1962) and by Grillmaier (1964).

Since Ac-228 is eliminated from the body at a negligible rate, the total-body Ac-228 measured by whole body counting is a measure of the total body Ra-228. Hence it is possible to relate the daily Ra-228 excretion to the total-body content of Ra-228, as done in section 2.2. This is not possible directly for Ra-224 since the whole-body activity of this nuclide may not be measured by whole-body counting. The actual Ra-224 content of the body is the sum of the activity of thoron (Rn-220) retained in the body (measured by whole-body counting of its descendant Tl-208) and the thoron activity maintained outside the body by exhalation (determined by breath measurements - see section 2.4.). Using this procedure to deduce the whole-body Ra-224 we find that the daily output of Ra-224 in the faeces is 1.62 % of the Ra-224 body burden (Kaul, 1965). Grillmaier (1964) found an excretion rate of 1.11 % per day. Even if somewhat lower, this value is comparable to ours since a variation of 30 - 50 % is observed in the daily Ra-224 excretion of even one patient (Kaul, 1965). The urinary Ra-224 excretion is about 1/100 as large, namely 2.2×10^{-2} %/day.

2.4. Exhalation of Rn-220

Stenstrom (1941) observed thoron for the first time in the breath of a Thorotrast patient. Later Kuth and Oberhausen (1962) published values indicating an exhalation of 9 - 10 % of the thoron produced in the entire body for patients with Thorotrast deposits in the liver and spleen, a result in good agreement with a value of 8 % given by Rundo et al. (1958) some years previously. Our own investigations yielded a value of about 10 % (Kaul, 1964; Kaul, 1965). Extensive recent investigations (Grillmaier et al., 1964a; Grillmaier, 1964)

clearly indicate for patients with exclusive liver and spleen deposits a mean result of 8 %, while in cases with additional high Thorotrast deposits at the sites of injection a lower value of 4 % was found. Further results will be discussed by Grillmaier and Muth at this meeting.

2.5. Excretion of Pb-212 with the urine

Our own measurements on a small number of cases indicated that about 0.8 % of the total amount of Pb-212 within the body of Thorotrast patients is excreted per day with the urine. Muth and Oberhausen (1962) previously found a value of about 0.15 %, while Grillmaier (1964b) reported an average result of 0.6 %.

2.6. Excretion of Th-228 with the faeces

A series of animal experiments indicate that Th-228 is excreted from the body, if at all, only at a low rate often close to the limit of detection. While Grillmaier (1964) has never observed a measurable excretion of Th-228 from the bodies of his Thorotrast patients, some of ours seemed to eliminate Th-228 at a rate of $\leq$ 0.008 % of the body burden per day (Kaul, 1965).

3. Steady-state activity ratios between members of Th-232 decay series

From excretion analysis we have seen that in the body radioactive equilibrium seems to be present only between Ra-228 and Ac-228 and between Pb-212 and its short lived daughters. (However, Bi-212 was found to be eliminated to a certain degree in one case of an extirpated spleen as described in section 3.3.). The measured excretion of Ra-228, Ra-224 and Rn-220 indicates that very marked degrees of radioactive disequilibrium exist between some of the members of the Th-232 decay chain in its steady state.

3.1. Steady-state activity ratios Bi-212/Ra-228 and Ra-224/Ra-228 as determined from whole-body counting

Since excretion of Ac-228 and Tl-208 is negligible, the γ-radiation from these nuclides as measured by whole-body counting reveals the activity in the body of their parents, Ra-228 and Bi-212. Values of the activity ratio Bi-212/Ra-228 in vivo have been reported as follows: 0.79 (Kaul, 1965); 0.65 - 0.71 (Rundo, 1956; Rundo, 1958); 0.79 - 0.84 (Muth and Oberhausen, 1962); 0.89 (Miller, 1958); 0.83 (Grillmaier, 1964); 0.93 (Dudley, 1964). Though Ra-224, Pb-212, and possibly Th-228 are excreted in measurable amounts, the chief cause of the disequilibrium of this ratio is thoron exhalation (section 2.4.).

If the total body Ra-224 is deduced by summing the activities of retained and exhaled thoron (section 2.3.), the ratio Ra-224/Ra-228 may also be determined. We have found a ratio of 0.9, while Grillmaier reported a value of 0.88. These values are consistent with the observed rate of excretion of Ra-224 from the body.

3.2. Steady-state activity ratio Th-228/Th-232 in samples of soft tissue

One may expect from the observed Ra-228 excretion a ratio of Th-228/Th-232 equal to about 0.5 (section 2.2.). Direct measurements of this quantity require assay of Th-232 by chemical or α-ray spectrometry methods, since Th-232 itself does not emit γ-radiation and its daughter Ra-228 has a half life too long (5.7 yr) to permit convenient establishment of equilibrium with the later γ-ray emitting members of the chain.

In our laboratory we have made numerous measurements of this ratio in biopsy or autopsy tissue samples from persons with long-term Thorotrast deposits. In our so-called "mixing method", the total α-ray activity and the Th-228 activity are determined by mixing ashed samples with ZnS(Ag) scintillator and observing the total α-ray counting rate and also the frequency of "coincidences" (i.e., short intervals) between the α-particles from Rn-220 and Po-216 (half life of Po-216 = 0.16 sec) (Stahlhofen, 1964; Stahlhofen and Kaul, 1964; Unnewehr et al., 1964).

Our results gave an average ratio of about 0.4. Similar results have been published by Parr (1964), although the duration of the burden in his patients was only 49 days. Various values of this ratio as reported in the literature are collected in Table 1. They show that in the liver and spleen, long-term deposits reach a steady state in which the Th-228/Th-232 activity ratio is about 0.5.

TABLE 1

Steady-state activity ratio Th-228/Th-232 in liver and spleen

Specimen	Activity ratio Th-228/Th-232	Method of analysis	Author
Liver	0.50	Growth of γ-ray counting rate	Rundo, 1956
Liver	0.45		Rundo, 1958
Spleen	0.57		
Spleen	0.40	Radiochemistry and α-ray analysis	Hursh, 1962
Liver	0.36	α- and γ-ray spectrometry; activity growth	Miller, 1962 Baserga et al., 1960
Spleen	0.31	α-ray coincidence technique	Stahlhofen and Kaul, 1964 Unnewehr et al., 1964
Spleen	0.31		
Spleen	0.66		
Liver	0.40		
Liver	0.40		
Average: 0.50 ± 0.12			

3.3. Steady-state activity ratios Th-228/Ra-228, Ra-224/Th-228, Pb-212/Th-228, and Bi-212/Th-228 in tissue samples

The ratio Th-228/Ra-228 can be measured in tissue samples by γ-ray spectrometry after allowing the short lived descendants of Th-228 to reach equilibrium. The available data for liver and spleen are collected in Table 2, and show an average value of 0.88. In perivascular deposits and in the kidney the ratio is close to unity (Kaul and Rajewsky, 1965; Oberhausen et al. (1964). The lower wash-out of Th-228 in such sites is attributable to the lower blood circulation.

TABLE 2

Steady-state activity ratio Th-228/Ra-228 in liver and spleen

Specimen	Activity ratio Th-228/Ra-228	Method of analysis	Author
Liver	0.80	Growth of γ-ray counting rate	Rundo, 1956 ✓ Rundo, 1958 ✓
Liver	0.73		
Spleen	0.83		
Spleen	0.96	Radiochemistry and α-ray analysis	Hursh, 1962 ✓
Liver	0.93	α-ray and γ-ray spectrometry; activity growth	Miller, 1962 ✓ Baserga et al., 1960 ✓
Liver	0.91	γ-ray spectrometry	Stahlhofen and Kaul, 1964 ✓ Kaul, 1965 ✓
Liver	0.87		
Liver	0.92		
Spleen	0.73		
Spleen	0.92		
Spleen	0.91		
Spleen	0.99		
Average: 0.88 ± 0.07			

Th-228 analogously shows lower wash-out in such circumstances for the same reason (Grillmaier, 1964; Muth and Oberhausen, 1962; Grillmaier et al., 1964).

The available results for the ratio Ra-224/Th-228, collected in Table 3, show less consistency in that they cover the range 0.6 - 0.9.

It is therefore not clear just what the usual metabolic behavior of Ra-224 is, and whether it depends on the duration of the Thorotrast burden.

TABLE 3

Steady-state activity ratio Ra-224/Th-228
in liver, spleen and kidney

Specimen	Activity ratio Ra-224/Th-228	Method of analysis	Author
Liver	0.66	Growth of γ-ray counting rate	Rundo, 1956
Liver	0.67		Rundo, 1958
Spleen	0.75		
Liver *	0.59	γ-ray spectrometry	Parr, 1964
Spleen *	0.75		
Liver *	0.65		
Spleen *	0.74		
Spleen	0.90	γ-ray spectrometry, growth of activity	Kaul and Rajewsky, 1965
Spleen	0.91		Kaul, 1964
Spleen	0.89		Kaul, 1965
Kidney **	0.80	γ-ray spectrometry, growth of activity	Oberhausen et al., 1964
Kidney **	0.81		

* Duration of Thorotrast burden 49 days.
** Kidney assumed to be equivalent to organs of the RES with regard to steady-state activity ratios between Th-232 daughters (Oberhausen et al., 1964).

The data reported on the activity ratio Pb-212/Th-228 are included in Table 4. Rundo's lower values may be explained in part by the higher wash-out of Ra-224 in his cases (Table 3).

Little information is available on Bi-212 equilibration. In one case of an extirpated spleen we found a ratio Bi-212/Pb-212 = 0.70, corresponding to a ratio Bi-212/Th-228 = 0.27 (Kaul, 1964; Kaul, 1965). Similarly, Parr (1964) found in rats a loss of 60 % Bi-212 from liver and spleen at 20 - 40 days after Thorotrast injection. Consequently, an assumption of equilibrium between Bi-212 and Pb-212 is not always justified.

TABLE 4

Steady-state activity ratio Pb-212/Th-228
in liver, spleen, and kidney

Specimen	Activity ratio Pb-212/Th-228	Method of analysis	Author
Liver	0.24	Growth of γ-ray counting rate	Rundo, 1956
Liver	0.27		Rundo, 1958
Spleen	0.13		
Spleen	0.40	γ-ray spectrometry, growth of activity	Kaul and Rajewsky, 1965
Spleen	0.40		Kaul, 1964
Spleen *	0.80		Kaul, 1965
Kidney **	0.38	γ-ray spectrometry, growth of activity	Oberhausen et al., 1964
Kidney **	0.40		

* Organ had shrunk to about half normal size.
** Kidney assumed to be equivalent to organs of the RES with regard to steady-state activity ratios between Th-232 daughters (Oberhausen et al., 1964).

4. Summary of data on excretion and steady-state activity ratios

The published data on the excretion of Th-232 and its longer-lived daughter products are summarized in Table 5, together with an estimate of average values. These values seem to be well established except for those on Th-228, which are given in parentheses.

In Table 4 are given published activity ratios between the longer-lived daughter products and Th-232 (normalized to unity). The estimated average values given in the last column are subject to a standard error of at least ± 20 %.

5. Calculation of the radiation dose in liver and spleen for various amounts of incorporated Thorotrast

5.1. Estimation of injected amount of Thorotrast

The amount of Bi-212(Tl-208) and Ra-228(Ac-228) in the liver and spleen, or at perivascular deposits, may be determined with an accuracy of 10 - 15 % by whole-body counting (section 1.2.). Simultaneous knowledge of the in vivo ratios Bi-212/Th-232 or Ra-228/Th-232 (sections 2 and 3) permits an estimate of the body's Th-232 content and thence the volume of Thorotrast injected.

TABLE 5

Elimination of Th-232 series radionuclides from the body

Nuclide	Published Values				Average Values			
	Faeces*	Urine*	Breath**	Reference	Faeces*	Urine*	Breath**	Comment
Th-232	$\geq 2.5 \times 10^{-4}$ $\leq 4.5 \times 10^{-4}$			Hursh et al., 1957 - " -	$\geq 2.5 \times 10^{-4}$ $\leq 4.5 \times 10^{-4}$			No further published values
Ra-228	2.6×10^{-2} 3.0×10^{-2} 3.4×10^{-2}	 1.4×10^{-3}		Hursh et al., 1957 Kaul, 1964 Grillmaier, 1964	3×10^{-2}	1.4×10^{-3}		Ditto
Th-228	($\leq 8.3 \times 10^{-3}$)			Kaul, 1965	($\leq 8.3 \times 10^{-3}$)			Uncertain
Ra-224	2.6 1.80 1.11	 2.2×10^{-2}		Hursh et al., 1957 Kaul, 1965 Grillmaier, 1964	1.8	2.2×10^{-2}		No further published values
Rn-220			8 10.9 4 - 8	Rundo et al., 1958 Kaul, 1965 Grillmaier, 1964 Grillmaier et al., 1964			8 4	Thorotrast mainly in RES Thorotrast mainly perivascular
Pb-212	0.83 0.6			Kaul, 1964 Grillmaier, 1964	0.7			

* % of body burden per day

** % of Rn-220 produced in body

TABLE 6

Steady-state activities in liver and spleen
(normalized to unity for Th-232)

Nuclide	Investigation					Average
	Rundo, 1956 Rundo, 1958 (average of 3 samples)	Hursh, 1962	Miller, 1962 Baserga et al., 1960	Kaul, 1965		
				autopsy and biopsy samples (Average)	excretion and/or whole-body meas. (Average)	
Th-232	1.00	1.00	1.00	1.00	1.00	1.00
Ra-228 (Ac-228)	0.65	0.48	0.41	0.45	0.52	0.50
Th-228	0.51	0.46	0.36	0.40	$\geq$0.48	0.45
Ra-224	0.35	-	-	0.36	0.44	0.38

Thus for activity measured in liver and spleen we assume: (1) Thorotrast contains 0.0222 μCi Th-232 per ml, (2) 0.7 of the Th-232 injected into the blood stream is deposited in liver and spleen, and (3) the steady-state activity ratios in liver and spleen are Ra-228/Th-232 = 0.45, Bi-212/Th-232 = 0.40. Combining these figures, 1 μCi Ra-228 or 1 μCi Bi-212 in liver and spleen correspond to the injection of:

$$1\ \mu\text{Ci Ra-228} \times \frac{1}{0.0222} \times \frac{1}{0.7} \times \frac{1}{0.45} = 143\ \text{ml Thorotrast}$$

$$\text{or}\quad 1\ \mu\text{Ci Bi-232} \times \frac{1}{0.0222} \times \frac{1}{0.7} \times \frac{1}{0.40} = 161\ \text{ml Thorotrast}$$

For perivascular deposits we assume an activity ratio Ra-228/Th-232 = 0.45, yielding for the equivalent volume of Thorotrast deposited perivascularly:

$$1\ \mu\text{Ci Ra-228} \times \frac{1}{0.0222} \times \frac{1}{0.45} = 100\ \text{ml Thorotrast.}$$

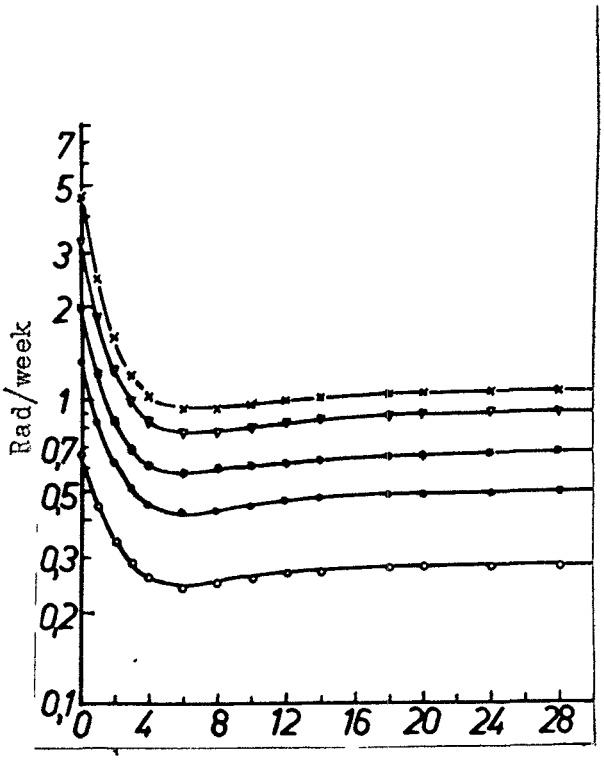
Applying such calculations to our cases, we have found estimated injected Thorotrast volumes in the range 10 - 100 ml. Agreement between calculations based on Ra-228 and those based on Bi-212 have been good. Usually the volume is not independently known from hospital records. However, in one case the volume injected 20 years ago had been recorded as 10 ml, an amount which was in excellent agreement with our calculated result of 10.1 ml.

5.2. Self-absorption of α-particles in ThO_2 aggregates

Several investigations (Berenbaum and Birch, 1953; Johansen, 1953; Ward, 1955; Guimaraes and Lamerton, 1956) have shown that the colloidal ThO_2 particles collect together in cells of the RES, eventually reaching aggregates as large as 100 μm in diameter. A Thorotrast volume of such dimensions absorbs much of the energy of the α-particles emitted within it, and the fraction of the energy dissipated in tissue itself is correspondingly reduced. Rotblat and Ward (1953) and Ward (1955) found that the average fraction of the α-particle energy dissipated in tissue surrounding these aggregates depends on the concentration of Thorotrast in the tissue. Rundo (1958) modified the corresponding formal expression on the basis of animal experiments (Guimaraes and Lamerton, 1956; Rundo and Hjort, 1953) so as to give the fraction as a function of time and thorium concentration.

5.3. Results of dose calculations

Combining the foregoing data, we have calculated the α-ray, β-ray, and γ-ray doses and dose rates in liver and spleen for different times after the injection of Thorotrast into patients. The following assumptions were made: (1) the activity ratio Th-228/Th-232 = 1 at injection, (2) practically no Ra-228 is injected, (3) the excretion rate of Th-232 and its daughter products is proportional to the amount present in the deposit at any given instant, (4) 52 % of the injected Thorotrast is deposited in the liver of mass 1700 g, while 17 % is deposited in the spleen of mass 150 g. Assumptions (1) and (2) may be



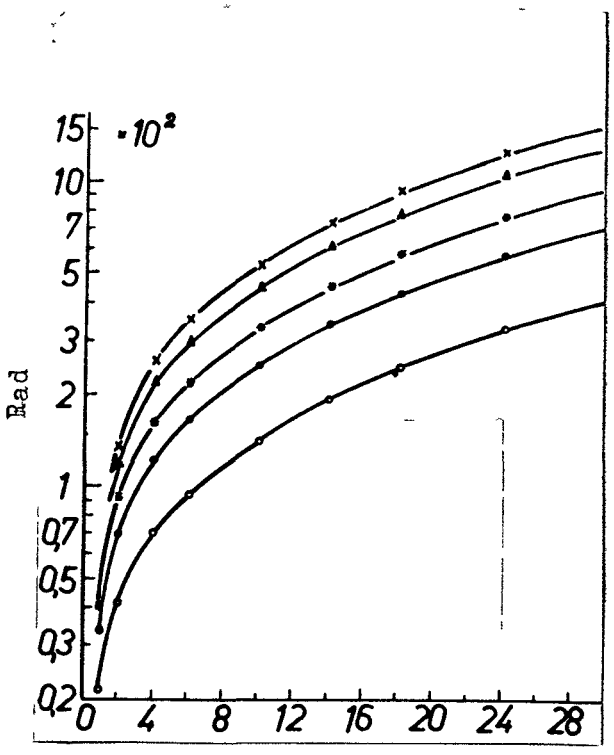
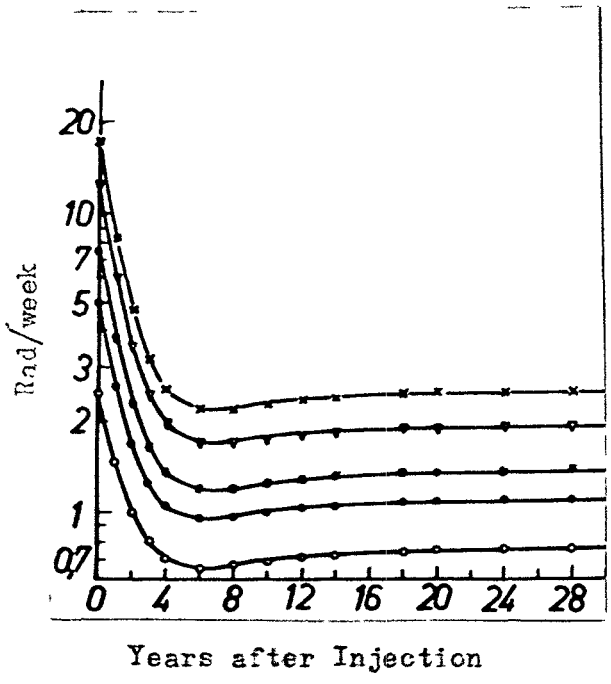


Fig. 1. Dose rate (left) and cumulative dose (right) in liver as a function of time after injection of various volumes of Thorotrast. Curves represent (top to bottom): 70, 50, 30, 20, or 10 ml.



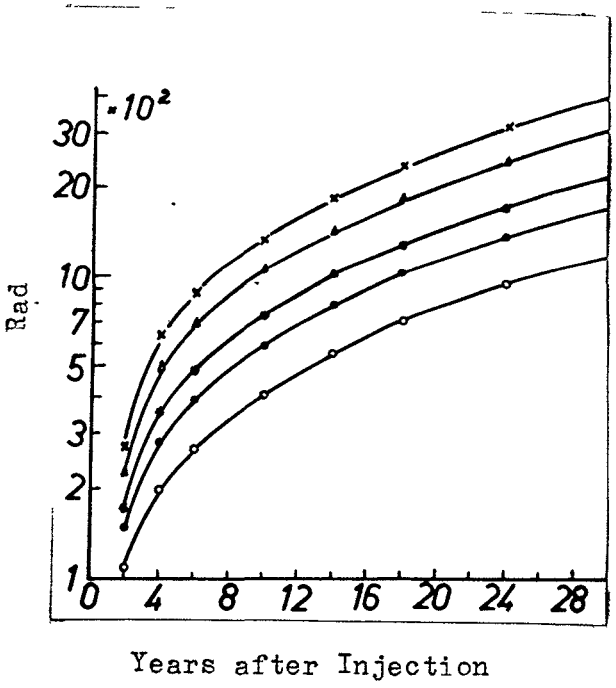


Fig. 2. Dose rate (left) and cumulative dose (right) in spleen as a function of time after injection of various volumes of Thorotrast. Curves represent (top to bottom): 70, 50, 30, 20, or 10 ml.

more or less valid, depending on conditions, as described by Parr at this meeting. Assumption (3) is only approximate, since the "constant" of proportionality may change with time. However, in dogs (Rajewsky and Muth, 1952; Muth, 1954) and in rats (Thomas et al., 1963; Boecker et al., 1963) it appears that the "constants" of proportionality for Ra-226 and for members of the Th-232 series do not change rapidly after the first few days. We have used numerical values consistent with the steady-state activity ratios of Table 6.

Fig. 1 shows, for liver tissue, the results of the calculations on the α-ray dose rate and accumulated dose as a function of time. (The α-ray dose is much greater than the ß-ray or γ-ray dose.) Fig. 2 shows corresponding data for the spleen. Twenty years after the injection of 20 ml Thorotrast, the α-ray dose rates are about 0.5 rad/week and 1 rad/week in liver and spleen, respectively, and the accumulated doses are about 500 rad and 1250 rad, respectively.

In Table 7 our results are compared with those of Rundo (1958) for a 20 ml injection. The difference of about 30 % between these values arises mainly from different assumptions about the percentage of the injected Thorotrast retained in liver and spleen: 70 % and 25 % by Rundo, 52 % and 17 % by us. In addition, the assumed steady-state activity ratios are not identical.

TABLE 7

Cumulative α-ray dose averaged throughout liver and spleen

Duration of burden (years)	Cumulative α-ray dose (rad) in: Liver (1700 g)		Spleen (150 g)	
	Rundo, 1958	Kaul, 1965	Rundo, 1958	Kaul, 1965
5	186	130	557	320
10	292	250	820	600
20	542	500	1428	1200

Finally, one may estimate the accumulated radiation dose to the liver in Thorotrast patients who have developed hepatic tumors of mesodermal origin. (These appear to be the predominant type of tumor in Thorotrast patients, just as bone tumors are the predominant type in Ra-226 cases (Looney, 1960; Faber, 1962).) In these cases, the mean period between Thorotrast injection and recognition of the tumor has been 15 - 20 years for an average incorporated amount of 60 ml. For a 15 yr burden our estimate of the accumulated dose in such cases is 800 rad, compared with 1000 rad from the calculations of Rundo (1958) and 1500 rad from those of Hursh et al. (1957).

6. Summary and discussion of results

(1) The total body burden of Ra-228 and Bi-212 in Thorotrast patients may be determined by whole-body counting with an accuracy of 10 - 15 %, whether or not a perivascular deposit remains at the site of injection.

(2) Th-232 and possibly Th-228 are excreted from the body at negligible rates, while measurable amounts of Ra-228, Ra-224, and Rn-220 are excreted or exhaled. The observed elimination rates are given numerically in Table 5, and the calculated or observed steady-state activity ratios established in the Th-232.decay series by this elimination are shown in Table 6.

(3) The dose rate in the tissue is also influenced by the self-absorption of α-ray energy in Thorotrast aggregates, the increasing size of the aggregates with increasing time since Thorotrast injection, and the continuous redistribution of aggregates in the deposits.

(4) Present knowledge suggests that a total average dose of about 1000 rad is delivered to liver tissue during the 15 - 20 years following injection of 60 ml Thorotrast. As Thorotrast is distributed very unevenly within the primary deposits, such that maximum local dose rates may exceed the average by a factor of at least 10, differences of about 50 % between the estimates of average dose rates published by different authors may be considered unimportant.

DOSIMETRY OF THOROTRAST IN LIVER, SPLEEN, AND BONE MARROW

K. Tsukamoto

In this report are summarized some of the dosimetric studies related to Thorotrast which have been conducted in Japan.

1. Measurements on tissue samples from humans

Tsuya et al. (1963) determined the thorium series content of human tissue by measuring the γ-ray and α-ray spectra of ash samples. The γ-ray measurements were made using a 1 3/4" x 2" NaI(Tl) well type scintillation crystal. Ten to 20 grams of organ sample were ashed, sealed in polyethylene tubes, kept for several weeks until the descendants of Th-228 reached equilibrium, and then measured by means of the 0.239 MeV γ-ray of Pb-212 or the 2.62 MeV γ-ray of Tl-208. For α-ray measurements the organ samples were ashed, suspended in distilled water with small amounts of ethyl alcohol, transferred to counting disks, evaporated to dryness, and counted with a gridded ionization chamber. These γ-ray and α-ray measurements yielded the activity of Th-228 and the Th-232/Th-228 activity ratios, respectively, and together, the quantity of Th-232 in the sample.

M. Miyakawa and H. Shibata, of Nagoya University, determined thorium by calorimetry, using Thorin, and compared some of their results with radiometric values determined by Kato. These data are shown in Table 1. There are considerable discrepancies among the values yielded by the two different methods.

From the radiometric results in Table 1 Kato calculated effective decay constants of Ra-228 in liver and spleen (assuming no thorium was excreted from these organs) of 0.234 yr^{-1} and 0.228 yr^{-1}, respectively.

Finally, the absorbed dose to the tissue has been calculated from the measured activities of these tissues and the further assumptions (1) that at injection the activity ratios in the thorium series were Th-228/Th-232 = = 1, Ra-228/Th-232 = 0, and (2) that in the liver 50 % of the α-ray energy is lost by self absorption in the Thorotrast while in the spleen 75 % is thus lost (Rotblat and Ward, 1953). The cumulative doses since injection are shown in Table 1.

2. Measurements on tissue samples from animals

S. Okawara of Nagasaki University made dosimetric studies on SM mice that had been injected with Thorotrast. One half ml of Thorotrast made 1½ years previously at Fellows-Testagar Co., U.S.A., was injected through a tail vein. The distribution of Thorotrast within the body and its excretion from the body were measured as a function of time by Thorin calorimetry. 20 % of the injected Thorotrast was excreted within 5 months.

Table 1

Thorotrast dosimetric data on human tissue samples

Case number	Purpose of roentgenography	Interval between injection and death (yr)	Interval between death and measurement (yr)	Mass of liver(L) and spleen (S) (g)	Data from Radioactivity Measurements				Data from Calorimetry	
					Th-228 conc. (dps/g)	Activity ratio Th-228/Th-232	Th-232 conc. (mg/g)	Cumulative dose (rad)	Th-232 conc. (mg/g)	Cumulative dose (rad)
1	Angiography	21	1.8	1250 (L)	3.5	0.58	1.5	470	1.8	560
				200 (S)	10.0	0.62	3.9	650	2.1	350
2	Hepato-lienography	21	3.9	900 (L)	11.4	0.60	4.6	1500	4.0	1300
				50 (S)	79.7	0.58	33.5	5600	—	—
3	Hepato-lienography	24	5.8	930 (L)	11.4	0.69	4.0	1500	9.8	3700
				40 (S)	107	0.56	44.1	8600	—	—
4	Hepato-lienography	19	3.7	890 (L)	20.5	0.61	8.2	2300	11.8	3400
				60 (S)	110	0.65	41.2	6100	—	—
5	Angiography	31	0.2	1060 (L)	1.6	0.34	1.2	580		
				45 (S)	25.0	0.36	16.9	4400		
6	Angiography	27	1.3	—— (L)	12.0	0.27	10.8	4700		
				—— (S)	84.0	0.40	51.1	11500		
7	Angiography	28(?)	0.4	790 (L)	3.5	0.32	2.7	1200		
				300 (S)	3.7	0.30	3.0	700		
8	Angiography	30(?)	0.3	1600 (L)	1.5	0.30	1.2	590		
				13 (S)	—	—	—	—		
9	Angiography	25	—	1160 (L)	—	—	—	—	1.9	740
				—— (S)	—	—	—	—	—	—
10	Hepato-lienography (?)	?	—	1000 (L)	—	—	—	—	8.0	—
				—— (S)	—	—	—	—	—	—
11	Angiography	28	—	1470 (L)	—	—	—	—	1.9	860
				160 (S)	—	—	—	—	4.0	930
12	Angiography	31	—	2000 (L)	—	—	—	—	2.9	1500
				180 (S)	—	—	—	—	4.8	1300
13	Angiography	29	—	2110 (L)	—	—	—	—	1.0	470
				40 (S)	—	—	—	—	16.3	4000
14	Angiography	32	—	1350 (L)	—	—	—	—	2.5	1300
				150 (S)	—	—	—	—	4.1	1100

90 % of all tissue-deposited Thorotrast was concentrated in liver, spleen, and bone, in the proportions 67 : 22 : 11 (Table 2).

Table 2

Excretion and distribution of Th in SM mice

Duration of burden	Excretion (mg)	Retention (mg)			
		Total	Liver	Spleen	Bone
4 hours	7	91	39	32	12
6 hours	17	81	50	26	11
1 days	18	80	37	25	10
3 days	18	80	41	20	11
2 months	19	79	50	15	7
3 months	19	79	46	18	7
4 months	20	78	48	19	7
5 months	20	78	48	13	10

Okawara also used a radiometric method to measure the amount of Thorotrast deposited in various organs. In this method he counted the equilibrated organs with a 2" x 2" NaI(Tl) well crystal, recording all pulses over 0.1 MeV. 17 % of the Thorotrast was found to be excreted within 24 hours after injection, and only 1 % was excreted in the next two days. 90 % of the Thorotrast still in the body after 3 days was in liver, spleen, and bone in the ratios 57 : 28 : 15. It is important to know the rate of excretion of thorium daughter products from an organ to estimate the total radiation dose to the organ. For this purpose Okawara measured the γ-ray activity of the extirpated organs of the animals 4, 14, 24, and 72 hours after injection, and plotted the build-up curve of the activity. He found that 71 % of the Ra-224 produced in the liver was released into the circulation, and 75 % of that produced in the spleen. On the other hand, the Ra-224 activity in the bones at sacrifice was somewhat higher than the Th-228 activity.

3. Measurements on Thorotrast in patients with a whole-body counter

Kato and others in our institute are investigating Thorotrast in patients with our whole-body counter. They have already examined 11 persons injected with known amounts. As a standard they used a Remab phantom (Alderson Research Labs, U.S.A.), with 3.98 g of aged Th (1906) in the "liver" and 0.80 g in the "spleen". The estimate of the amount of Th-232 in the patients was made on the basis of the 0.91 MeV γ-ray emitted from Ac-228 (to avoid uncertainties associated with the excretion of Th-232 descendants), coupled with an assumption taken from Table 1 that the

ratio of activities Ac-228/Th-232 = Th-228/Th-232 = 0.39. In order to distinguish between the Th series γ-ray emitters contained in the liver and spleen, each subject was measured first with the detector positioned against his right side (liver), second with the detector against his left side (spleen). By comparing these count rates with those measured equivalently on the phantom (having known "liver" and "spleen" contents), a calculation was possible for the separate liver and spleen activities of each subject (Table 3).

By determining the counts from Ac-228 and Tl-208 from the subjects and from the phantom, it was deduced that the ratio Tl-208/Ac-228 averaged 25 % lower in the subjects than in the phantom. It therefore is likely that some of the daughter products of Ac-228 are released from the liver and spleen into the circulation.

Kato and associates estimated the α-ray dose in liver and spleen tissue of the living patients by assuming (1) organ weights of 1200 g and 100 g, respectively, and (2) daughter product equilibrium status and self absorption of α-ray energy in Thorotrast aggregates as for the tissue sample calculations. The cumulative doses deduced are included in Table 3.

Table 3

Thorium body burden of 11 patients measured in whole-body counter

Case number	Injected amount (ml)	Interval between injection and measurement (yr)	Organ	Th content of organ (g)	Dose (rad)
1	5	28	L. S.	— 	—
2	8	28	L. S.	1.00 0.30	370 700
3	10	28	L. S.	0.48 0.12	180 280
4	10	28	L. S.	0.63 0.17	230 290
5	10	27	L. S.	0.97 0.13	360 300
6	15	26	L. S.	3.38 0.82	1200 1800
7	15?	26	L. S.	2.66 0.44	900 930
8	20?	27	L. S.	1.61 0.39	590 880
9	20	28	L. S.	3.01 0.79	1100 1800
10	25	28	L. S.	3.84 0.96	1400 2200
11	36?	25	L. S.	4.39 0.61	1500 1300

DOSE IN TISSUE AFTER LOCAL ADMINISTRATION OF THOROTRAST: PERIVASCULAR INJECTIONS, RETROGRADE PYELOGRAPHY

E. Oberhausen

1. Introduction

There has been reported in the literature a great number of Thorotrast cases with perivascular injections. Unfortunately, the radiation dose has been measured in only a few. There are several reasons for the difficulties in determining the radiation dose.

(1) It is practically impossible to remove a perivascular infiltrate of Thorotrast completely.

(2) Even if one has a pathological specimen of a perivascular infiltrate it is not easy to determine the radiation dose in that tissue, since the radiation dose is to a high degree determined by the thoron and its daughter products. Therefore it is necessary to know how these nuclides behave and to what extent radioactive equilibrium in the thorium decay series exists in the perivascular infiltrate.

(3) Most of the radiation dose is delivered by α-particles. Therefore it is necessary to know how much self-absorption takes place within the thorium dioxide aggregates.

(4) The Thorotrast is not uniformly distributed throughout a perivascular infiltrate, and the dose rate in some regions may therefore be much higher than in others.

In view of these problems one must combine several measurement procedures to obtain realistic values for the radiation dose. Up to now this has been done for only a few cases.

In contrast to the perivascular infiltrates resulting from false injections, very few cases with Thorotrast deposits in the kidney have been reported. This is surprising because Thorotrast has for many years been used very often in retrograde pyelography. This lack of reports may have several explanations:

(1) In a pyelography made in a normal way the Thorotrast should afterwards be completely eliminated with the urine. There is no possibility that a deposit is formed. Deposits have probably been formed only if at the time of retrograde pyelography there was an inflammation of the pelvis of the kidney, or if the contrast medium was applied under too high pressure.

(2) Very often deposits of Thorotrast in the kidney are not recognized, because on the x-ray picture they look like calcification which frequently occurs as a result of tuberculosis in the kidney. Therefore we think that the number of Thorotrast patients with deposits in the kidney is much higher than suggested by the number reported in the literature.

We have previously reported on 7 cases with Thorotrast deposits in the kidney (Oberhausen et al., 1964). These 7 cases we saw between 1958 and 1964. They came from a total population of about 5×10^5 persons. During the last year we have seen three further cases. One had a deposit in both kidneys, but as yet the patient has shown no clinical symptoms. In the second case there was clinical evidence of a carcinoma of the kidney and a nephrectomy was planned. However, during medical examination it became evident that the patient already had metastases in other organs, and the nephrectomy was therefore not made. The third case has the smallest deposit of Thorotrast we have ever found: about 10^{-9} Ci Ra-228. This patient shows no clinical symptoms.

The same difficulties which exist in evaluating the radiation dose in perivascular infiltrations are also present for deposits in the kidney. But in most of the kidney cases we have found, a nephrectomy has been performed since there was clinical evidence of a carcinoma. Therefore we have had the opportunity to make autoradiographic and spectrometric measurements on isolated organs. Also, it has sometimes been possible to measure the total deposit in the patient by whole-body counting before and after kidney extirpation, giving a check on the activity of the kidney in vivo.

2. Perivascular deposits

Schwaiger et al. (1949) determined the concentration of Th-232 itself in perivascular deposits by observing the attenuation in the tissue of a beam of low-energy γ-rays (in their case, from Pb-210). In animal experiments they were able to measure Th-232 concentrations of 0.06 - 0.2 g/cm^3, and in a human case 0.3 g/cm^3. The concentration of the other members of the Th-232 decay series was determined in animals by measurements on the α- and β-rays emitted in the tissue sample. As the α- and β-ray activity increased with time after extirpation with the half life of Ra-224, they concluded that in vivo the Ra-224 activity was lower than that of Th-228. They reasoned therefore that the longer lived radium isotope, Ra-228, should also be greatly depleted. In older deposits they expected that fibrosis would cause the retention of a higher fraction of the decay products.

Brady et al. (1960) made measurements by γ-ray spectroscopy on the thorium series activity in a sample of a perivascular deposit surgically removed from the neck of a patient. They estimated a Th-232 concentration of 0.018 g/cm^3 tissue, a value which agreed with that calculated from the total volume of Thorotrast injected (known from records) and the total volume of tissue containing the deposit (estimated by radiography). Thierbach et al. (1960) measured the thorium content of a tissue sample by comparing the total α-ray activity in its ash with that of normal tissue ash to which a known amount of 20 year old ThO_2 had been added. As the old ThO_2 certainly contained a higher proportion of the daughter products than did the tissue, the measured thorium concentration of 0.0023 g/cm^3 in the tissue would have been an underestimate.

In several papers the dose is calculated according to the measured thorium concentration, or that estimated from radiographs or injection records, under the assumption of radioactive equilibrium in the series. However, direct measurements show that equilibrium does not exist. Thus

Kaul (1964) found in two pathological specimens the following activity ratios: Th-228/Ra-228 = 0.96, Ra-224/Th-228 = 0.9, Pb-212/Th-228 = 0.52.

Our own measurements give indirect evidence on the daughter product equilibrium status. Seven out of our total of 59 patients had perivascular deposits only. In all these we have the following data: (1) Ra-228 and Tl-208 in body measured with a whole-body counter, (2) Rn-220 (thoron) concentration in exhaled air, (3) Pb-212 and Ra-224 content of blood, (4) Ra-228, Ra-224, and Pb-212 excretion in urine, and (5) Ra-228 and Ra-224 excretion in feces. From these results and from physiological data, Grillmaier (1964) has calculated the probable activities of the different daughter products in old deposits (20 years), expressed as a percentage of their Th-232 activity: Ra-228 through Th-228 = 48 %, Ra-224 = 46 %, Rn-220 and descendants = 40 %. It is thus clear that even in old deposits the Ra-228 is present only at about half of equilibrium as a result of wash-out and in young deposits its activity would be still lower due to its depletion in the Thorotrast at injection (Rundo, 1955). A small percentage of Ra-224 and thoron escapes from the deposits. While we have not detected further wash-out of Bi-212 and its successors, their half lives are too short to permit reliable measurement. Grillmaier's indirect deduction that Pb-212 is retained in the deposit (Pb-212/Th-228 = 40/48 = 0.83) does not agree well with Kaul's measurements (Pb-212/Th-228 = 0.52); this point requires further investigation.

Assuming Grillmaier's results on activity ratios in the thorium series, one calculates that a concentration of 0.1 g Th-232 per gram of tissue corresponds to a dose rate of 10.1 rad/day from α-rays emitted by a 20 year old deposit. This value must be further corrected for the self-absorption of α-ray energy within the Thorotrast aggregates. Taking this correction factor as given by Rotblat and Ward (1953), one reaches a final value of 2.5 rad/day. Therefore the radiation dose rates in perivascular deposits reported in the literature are between 0.06 and 7.5 rad/day.

3. Kidney deposits

Vögtlein and Minder (1952) found in Thorotrast deposits in the kidney after retrograde pyelography the following thorium concentrations: 14 mg/g tissue for regions where Thorotrast deposits could be seen, 3 mg/g elsewhere.

In our own work we have sought information regarding the daughter products by a combination of γ-ray spectrometry and autoradiography on isolated organs (Oberhausen et al., 1964a). Gamma-ray spectrometry over a period of several days after the extirpation gives the activity of Th-228 and its daughters. The subsequent quantitative autoradiography gives the activity ratio between Th-228 and Th-232.

On two patients (E.M. and M.H.) we determined by whole-body counting the Ra-228 and Bi-212 burdens prior to surgical removal of the kidney (using the γ-radiation of their daughters Ac-228 and Tl-208). On the extirpated kidneys gamma-ray spectrometric measurements were started immediately after surgery and continued during a period of 3 months. (In one case we selected the 560 keV γ-ray peak, in the other the 2.6 MeV peak). The activity was found to increase with the half lives of Ra-224 and Pb-212,

and by analysis of the growth curves the equilibrium status of the Th-228 daughter products at the time of extirpation of the kidneys could be calculated. The results of these measurements are shown in Table 1. It is evident from the Ra-228 data that only about half of the total Thorotrast burden in the body was located in the kidneys; radiographs of the patients revealed that most of the remainder was contained in the perivertebral lymph nodes. It is also evident that high percentages of the Th-228 daughter products are washed out of the kidney. As we found in the expired air 13 % of the Rn-220 (thoron) produced in the body, the depletion of Pb-212 may be inferred to result mainly from the escape of thoron from the Thorotrast aggregates.

TABLE 1.

Thorium series nuclides in retrograde pyelography cases

	Patient E.M.	Patient M.H.
Total body activity before extirpation		
Ra-228	8.2 nCi	5.0 nCi
Bi-212	7.5	4.4
Kidney activity at extirpation		
Ra-228	3.9 nCi	2.4 nCi
Th-228	3.9	2.3
Equilibrium status at extirpation		
Ra-224/Th-228	0.80	0.81
Pb-212/Th-228	0.38	0.40

To find the activity ratio Th-228/Th-232 we used quantitative autoradiography. The method is based on the fact that the length of an α-ray track is approximately proportional to the energy of the α-ray. Therefore the distribution of track lengths in an autoradiograph reveals the relative abundance of the different α-ray emitters in the tissue section from which the α-rays emerge. The detailed analysis is of course complicated: only a part of each α-ray track appears in the photographic emulsion, the rest being invisible in the tissue section itself. However, quantitative information can nevertheless be mathematically deduced from measured track length distributions (Roucayrol and Oberhausen, 1961), giving the Th-228/Th-232 activity ratios in the tissue. In measurements on our two cases we inferred ratios of 0.11 and 0.14, respectively. These low values can be explained only if a much higher fraction of Ra-228 escapes from Thorotrast deposits in kidneys than from deposits in other tissues. By combining the γ-ray spectrometric and the autoradiographic measurements, one obtains the following relative activities of the thorium series α-ray emitters in the kidney: Th-232, 100 %; Th-228, 14 %; Ra-224, 11 %; Rn-220, 6 %; Po-216, 6 %; Bi-212, 2 %; Po-212, 3 %.

From x-ray pictures of the isolated organs we estimated in these two cases that the Thorotrast is contained in only 1/40 of the tissue of the total kidney. If one further assumes that only 25 % of the α-ray energy

is deposited in tissue (the rest being absorbed in the Thorotrast aggregates), one obtains the following tissue dose data: (1) dose rate at time of extirpation - 4.2 rad/week (E.M.) and 2.8 rad/week (M.H.), (2) cumulative dose since Thorotrast incorporation (assuming constant dose rate) - 5900 rads (E.M.) and 4200 rads (M.H.).

In two other cases where we were unable to do γ-ray spectrometry, we derived the dose from counting the α-tracks over a measured area of the slides (Alken et al., 1960 and 1961). The dose estimates were very comparable to those for cases E.M. and M.H..

METABOLISM AND LOCALIZATION OF THORIUM SERIES NUCLIDES AFTER ENTRY INTO BLOOD IN IONIC FORM: OBSERVATIONS IN ANIMALS

B. J. Stover and D. S. Buster

1. Introduction

Studies of the metabolism and biological effects of thorium in laboratory animals began within a few years after the discovery of this radioactive element. Two papers which appeared in 1906 reported on the oral, intramuscular and intravenous administration of thorium nitrate and thorium citrate to dogs and rabbits (Sollman and Brown, 1906), and thorium chloride by various routes to dogs and frogs (Chace and Gies, 1906). However, these and other early researchers were plagued with analytical problems of such severity that very few of the results are of value. For this reason the early work will not be considered further.

More recent work has shown that there are two features of the metabolism of the thorium series that are of primary importance for dosimetric considerations. The first is that the distribution of thorium in the animal after entry into the blood in what appears to be ionic form is a function of the number of atoms of thorium given. The second is that the decay products in part leave the sites at which they are formed to decay at other sites in the animal or to be excreted to decay outside the animal. The fractions of the decay products that are excreted are fairly small. The main effect on the dosimetry is that unknown fractions of the decay products release their energy at unknown sites in the animal.

2. Distribution of thorium

The metabolism of the Th-228 (RdTh) decay series in dogs is being studied at the University of Utah. This work is part of a program to compare the long term effects of Ra-226, Pu-239, Ra-228, Th-228 and Sr-90 in adult beagles (Dougherty et al., 1962). The objective of the excretion and distribution studies is to provide information for use in estimating radiation dose rates to specific tissues or parts of tissues.

Each young adult dog received a single intravenous injection of Th-228 in citrate buffer, 0.08 M in total citrate, pH = 3.5 (Stover et al., 1960). Analysis of the Th-228 stock solution showed that it also contained some longer-lived isotopes of thorium. The material given the dogs contained from 0.08 to 0.5 μg Th/μCi Th-228. The concentration in blood plasma, daily urinary and fecal excretion, and the amounts in liver, spleen, kidneys, one humerus and the third lumbar vertebra were measured through 3.5 years after injection. In addition, nine dogs sacrificed 1 to 910 days after injection were measured so that the Th-228 in the selected bones and soft tissues listed above could be related to total Th-228 in bone and in soft tissues. The presently available results are summarized in Table 1 (Stover et al., 1960; Stover et al., 1965; Stover et al., 1965a). (The equations for P, U, X and R are for 100 days $\leq t \leq$ 3.5 years. For $t <$ 100 days the rates of decrease are greater). The excretion rates decrease

Table 1

Biological decrease of the Th-228 decay series in beagles [a]

	Th-228	Ra-224	Pb-212	Bi-212	Units [b]
Concentration in blood plasma	$P = 2.3 \times 10^{-5} e^{-0.0013t}$	$= 5.6 \times 10^{-4} e^{-0.0013t}$	-----	~ 2P (Ra-224)	%/g, days
Concentration in blood cells	C -----	-----	$= 0.0110 e^{-0.00097t}$	~ 0.9C(Pb-212)	%/g, days
Daily excretion					
Urinary	$U = 0.019 e^{-0.0018t}$	$= 0.68 e^{-0.00092t}$			%/day, days
Fecal	F -----	$= 1.16 e^{-0.00053t}$			%/day, days
Total	$U+F=X=0.021 e^{-0.0011t}$	$= 1.87 e^{-0.00075t}$			%/day, days
Amount in					
Liver	$L = 4.0 e^{-0.00094t}$	$= 5.2 e^{-0.0010t}$	$= 5.4 e^{-0.0010t}$		%, days
Spleen	$S = 0.32 e^{-0.0010t}$	$= 0.34 e^{-0.0011t}$	$= 0.16 e^{-0.00091t}$		%, days
Kidneys	K = 0.99	= 0.28	= 0.28	= 1.16	%, days
One humerus	H = 2.86	= 2.67	= 2.55		%, days
Third lumbar vertebra	$V = 1.2 e^{-0.00025t}$	= 0.97	= 0.94		%, days
Both bones	$H+V=4.2 e^{-0.0014t}$	= 3.64	= 3.53		%, days
Bone	$B = 69 e^{-0.00014t}$	$= 62 e^{-0.00014t}$	$= 60 e^{-0.0014t}$		%, days
Retention	$R = 18 e^{-0.0010t} + 69 e^{-0.00014t}$	$= R(\text{Th-228}) - 10.8 e^{-0.00075t}$	~ 0.97R(Ra-224)	~ 0.96R(Ra-224)	%, days

a) Stover et al., 1960; Stover et al., 1965; Stover et al., 1965a

b) $\% \text{ Th-228, Ra-224, Pb-212, or Bi-212} = \dfrac{\mu\text{Ci Th-228, Ra-224, Pb-212, or Bi-212 in sample} \times 100\ \%}{\mu\text{Ci Th-228 injected} \times e^{-(\lambda \text{Th-228})t}}$

where t is time in days since injection.

rapidly soon after injection. In 22 days an average of 12.4 % was excreted, 80 % of which was in the urine and 20 % in feces. Later the fecal to urinary ratio increased to about unity.

Of the retained Th-228 about 80 % was in bone and the remaining 20 % was distributed throughout soft tissues. Roughly 1/4 of the soft tissue Th-228 was found in liver and spleen.

Radioautographic studies by Jee et al. (1962) have shown that the microscopic distribution of Th-228 in the bone of these dogs is similar to that of Pu-239. The initial deposits are on mineralized bone surfaces (periosteum, endosteum, resorption cavities, forming osteons, Volkman and haversian canals and vascular channels). The initial pattern is gradually altered by the continuous bone remodelling processes. Apposition of new bone results in burial of the surface deposit. When the surface is resorbed, the Th-228 goes to osteoclasts and macrophages and also appears in low concentration in bone being formed at that time. Autoradiograms of selected soft tissues showed that Th-228 deposits in the reticuloendothelial cells of the liver, diffusely throughout the kidney with higher concentrations in the renal papillae, and in the aortic media.

Earlier Hamilton (1948) had reported the metabolism of carrier-free Th-234 in rats. Bone was the principal site of deposition and autoradiograms of bone showed a microdistribution like that of Pu-239. Thus, these short-term results in rats were consistent with the results of the more extensive studies in beagles (Stover et al., 1960; Jee et al., 1962).

In contrast, Engels et al. (1949), Salerno and Mattis (1951) and Scott et al. (1952) observed that the major part of thorium was deposited in soft tissues after intravenous injection. The principal difference between these studies and those in which bone was the main deposition site was the amount of thorium injected. Engels et al. reported the distribution of varying amounts of $Th(NO_3)_4$ tagged with Th-234 at 24 hours after injection. Some of their data showing the effect of the amount injected on liver deposition are given in Table 2.

Table 2

Percent injected Th in liver at 24 hours
(Data from Engels et al., 1949)

Amount Injected	Rabbit	Rat	Pigeon
10^{-11} g	18.8 %	---	---
10^{-6} g	---	---	12.5 %
2×10^{-3} g	68.0	57.3 %	65.1
5×10^{-3} g	---	74.2	---

Table 3

Percent of injected thorium in organs and excreta of rats and guinea pigs after intravenous administration

Average of two animals in each group
(Data from Scott et al., 1952)

Species	Days After Injection	Liver	Spleen	Kidney	Gastro-Intestinal Tract	Carcass*	Feces	Urine	Other Organs
Rat	1/4	56.2	2.2	0.4	3.7	9.4			28.1
Rat	1	77.4	2.9	0.4	3.0	10.4	0.7	0.0	4.7
Rat	2	78.2	4.0	0.4	5.5	7.5	1.5	0.0	2.9
Rat	3	73.5	2.7	0.3	3.6	7.2	8.8	0.3	3.3
Rat	14	45.5	1.5	0.3	0.8	10.5	32.8	4.9	3.5
Rat	42	50.4	6.8	0.3	2.9	11.4	24.5	3.6	0.1
Guinea pig	2	72.3	9.9	0.2	3.5	11.6	0.6	0.0	1.9
Guinea pig	5	64.7	4.5	1.9	2.6	9.2	14.6	1.2	1.3

* Mainly bone

In their experiments Scott et al. (1952) injected solutions of $Th(SO_4)_2$ tagged with Th-234. The doses averaged 2.5 mg $Th(SO_4)_2$/kg with a range of 1.5 to 4.0 mg/kg. Their observations on distribution of Th in rats and guinea pigs are given in Table 3. The liver is the principal site of deposition with only 10 % or less in the skeleton. Also of interest is their comparison of the concentrations in several tissues from rabbits sacrificed 1 to 6 days after injection. The tissue concentrations (%/g) are: liver, 0.5; spleen, 0.9; bone marrow, 0.4; and cancellous bone, 0.08.

Boone et al. (1958) studied the toxicity of Th-230 in rats. The thorium was given in citrate solution and contained considerable Th-232. The atom ratio was Th-232/Th-230 = 7.94 ± 0.16. The amount of Th administered ranged from 9 to 60 mg/kg, and, as shown in Table 4, liver deposition was nearly constant but skeletal deposition increased with increasing amount of thorium.

Table 4

Tissue distribution of Th-230 (Io) following intravenous administration to the rat (percentage of injected dose) (Data from Boone et al., 1958)

Dose µCi/kg Body Wt.	Number Animals	Skeleton	Liver	Spleen	Kidney	Balance	Total Soft Tissue
130	6	37.2	14.3	2.10	4.2	19.1	39.1
108	6	35.0	11.0	0.27	1.8	17.9	31.0
86.9	3	33.8	11.3	0.78	1.4	18.8	32.3
38.6	8	25.6	13.7	1.10	1.2	32.7	48.6
29.0	5	17.7	13.1	1.15	1.2	37.0	52.5
19.3	2	19.7	13.9	--	--	38.5	52.4

Limited studies were made in beagles of the effect of amount injected on the distribution pattern and the results appear in Table 5 (Stover et al., 1960a). The Th was given in 0.08 M citrate buffer, pH = 3.5. These studies were not pursued further since Thomas et al. (1963) were then doing studies of the effect of route of administration and of the amount given in rats. Thomas et al. (1963) analyzed the available data on skeletal deposition of thorium in the rat following intravenous injection. These are shown in Fig. 1, taken from their paper. Of further interest are the inhalation studies using rats reported by Boecker et al. (1963) and Boecker (1963). The thorium that moved from the lungs of the rats to the blood was deposited mainly in the skeleton analogous to the pattern when "tracer" amounts were given intravenously.

The above biological data suggest that when thorium is introduced into the blood by injection of very small amounts, or reaches the blood at a slow rate from other sites such as the lungs, the thorium ions interact mainly with ions and molecules of the animal. As the amount is increased

Table 5

Effect of amount of thorium injected: a 22 day comparison in beagles

Dog(s)	Wt. Th Injected (mg)	Total Excretion % Dose	Feces / Urine	Liver % Dose	Kidneys % Dose	Spleen % Dose	Humerus % Dose
T11T3	40	16	1.5	32	2.2	3.9	1.3
T12T3	4.0	14	0.48	38	1.2	2.8	0.8
T13T3	0.40	12	0.47	40.	2.0	1.7	0.8
Av. Th-228	$\sim 10^{-3}$	12±3	0.25	4.0	1.4	0.3	2.9

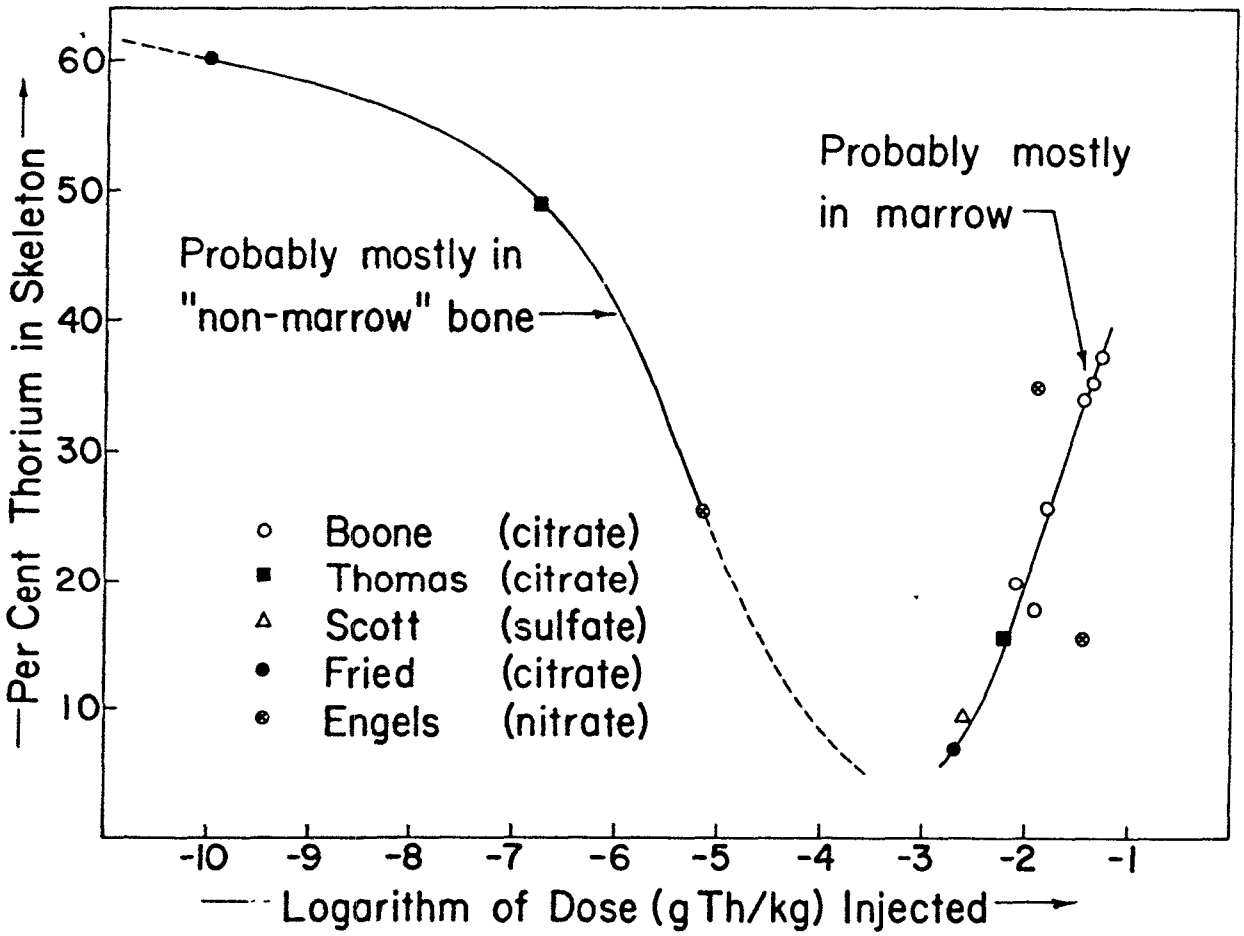


Fig. 1. Percent deposition in the skeleton of rats as a function of the quantity of intravenously injected thorium (Thomas et al., 1962)

the thorium ions interact to form colloidal particles which deposit in the reticuloendothelial cells of liver and spleen and of the bone marrow. An important unanswered question is whether the aggregation of thorium into colloidal particles occurs during the preparation of the injection solution and/or in the blood of the animal.

Colloidal thorium hydroxide has been prepared and characterized by Dobry et al. (1953). It was prepared by hydrolyzing dilute solutions (0.2 - 2 %) of $ThCl_4$ or by adding NH_4OH to $ThCl_4$ to the point of incipient precipitation. Then H^+, Cl^-, and NH_4^+ in the latter case, were removed by dialysis. The macromolecules were probably of the form of a chain: $(Th(OH)_2O)_nTh(OH)_3Cl$. The electron microscope showed filaments of length 150 to 2500 Å (av. 700 Å) and diameter about 18 Å, and also some spheres. Long filaments were demonstrated by birefringence, while light scattering and viscosity indicated spherical particles which could be coiled filaments. Diffusion data gave molecular weights of 175,000 to 960,000 compared with 2.6 to 4.0 x 10^6 calculated from dimensions. The 18 Å diameter corresponds to a bundle of 20 or 30 of the above chains.

How do these results relate to the distribution of thorium in animals? Since rather special techniques are required to observe the presence of colloidal thorium hydroxide, it is possible that the solutions used in the intravenous studies cited above contained varying amounts of colloidal material. In some the pH of the thorium solutions was raised by adding NaOH solution. When this is done there are small regions of very high pH which are conducive to colloid formation. In another case thorium was precipitated as the hydroxide during one step of the preparation, and it is possible that some colloidal material remained when it appeared visually that all of the thorium had been redissolved. These considerations lead to the conclusion that the effect of the amount of thorium injected on the distribution may result from the nature of the material injected and hence is not a biological interaction.

The particles observed by Dobry et al. (1953) are small compared with cells, e.g., 0.07 μm x 0.018 μm, but they are large compared with lattice sites on bone crystals. Their molecular weights are of the order of magnitude of those of some of the larger blood proteins.

Thus it appears that a spectrum of distribution of thorium is possible since there is a spectrum of thorium species ranging from simple labile complexes through dimers and polymers of gradually increasing size to the fine particles of Thorotrast suspensions.

3. Excretion and distribution of Ra-224 formed in vivo

Although there have been other investigations of Ra-224 formed in the animal by decay of Th-228, this section will be limited to the long-term studies done in beagles. Van Dilla et al. (1957) reported the excretion and translocation of Ra-224 in dogs given Th-228 through 110 days after injection. These early results suggested that the excretion of Ra-224 might substantially reduce the potential radiation dose rate (analogous to the effect of Rn-222 exhalation on Ra-226 radiation dose rate) and further that translocation would result in a more uniform dissipation of energy in the skeleton. For these reasons, more extensive long-term measurements were undertaken (Stover et al., 1965; Stover et al., 1965a). The results showed that no substantial reduction in radiation dose rate results from

excretion of Ra-224 but that translocation of Ra-224 does affect the pattern of energy dissipation. These results are summarized in Table 1, which gives plasma concentration, excretion rates, distribution, and retention equations.

At 3 to 4 weeks after injection of Th-228 (with its decay products in equilibrium), essentially all of the Ra-224 in the animal was formed there. At this time average cumulative excretions were 11 % (Th-228) and 35 % (Ra-224), so that 0.65 x 100/0.89 = 73 % of the Ra-224 formed in the dog decays there. Throughout 3.5 years Ra-224 continues to be excreted. The fractional retention of Ra-224 formed in vivo is given by the following equation:

$$f = \frac{R(\text{Ra-224})}{R(\text{Th-228})} = 1 - \frac{1}{1.67e^{-0.00025t} + 6.39e^{+0.00061t}} \quad . \quad (1)$$

At 100, 500, and 1000 days, Eq. (1) gives f = 0.88, 0.90, and 0.92, respectively, and approaches unity as t increases without limit. Thus only about 10 % of the Ra-224 produced in vivo is excreted during about 2 Th-228 half-periods, so that there is no marked reduction in the potential radiation dose rate.

The fraction of Ra-224 = F_t(Ra-224) that undergoes translocation within the dog can be calculated if it is assumed that each translocating Ra-224 atom goes quickly to the blood and there acts as though it had been injected intravenously (Stover et al., 1965a). The results of the calculation of F_t(Ra-224) are shown in Fig. 2. F_t(Ra-224) decreases with time. Of the translocating Ra-224 atoms 1/3 are excreted and 2/3 redeposit in the animal.

Since most of the Th-228 is in bone most of the translocating Ra-224 comes from bone. Some redeposits in bone in a typical alkaline earth pattern (Van Dilla et al., 1957), and some goes to soft tissues. The net effect is that Ra-224 activity is less than that of Th-228 in bone and kidneys, and it is greater in blood plasma, liver, spleen, and perhaps some other soft tissues (Stover et al., 1965). These results are summarized in the equations of Table 1.

4. Excretion and distribution of Rn-220 and subsequent decay products

The 3.64 day half-period of Ra-224 is sufficiently long that quantitative information can be obtained for the calculation of average radiation dose rates to tissues of interest, and qualitative information can be obtained on the microdistribution of Ra-224 by making autoradiograms immediately after sacrifice of the animal. The half-periods of the subsequent nuclides are all shorter. This limits the measurements that can be made.

Following Ra-224 the next member is the inert gas nuclide Rn-220 (54.5 sec half-period). The exhalation of Rn-220 by beagles injected with Th-228 and with Ra-228 has been reported by Mays et al. (1958). They found that the fraction exhaled is small and that it decreases both with increasing time after injection and with increasing radiation dose rate. Since little is exhaled, a satisfactory estimate of the retention of Rn-220 by beagles given Th-228 is given by

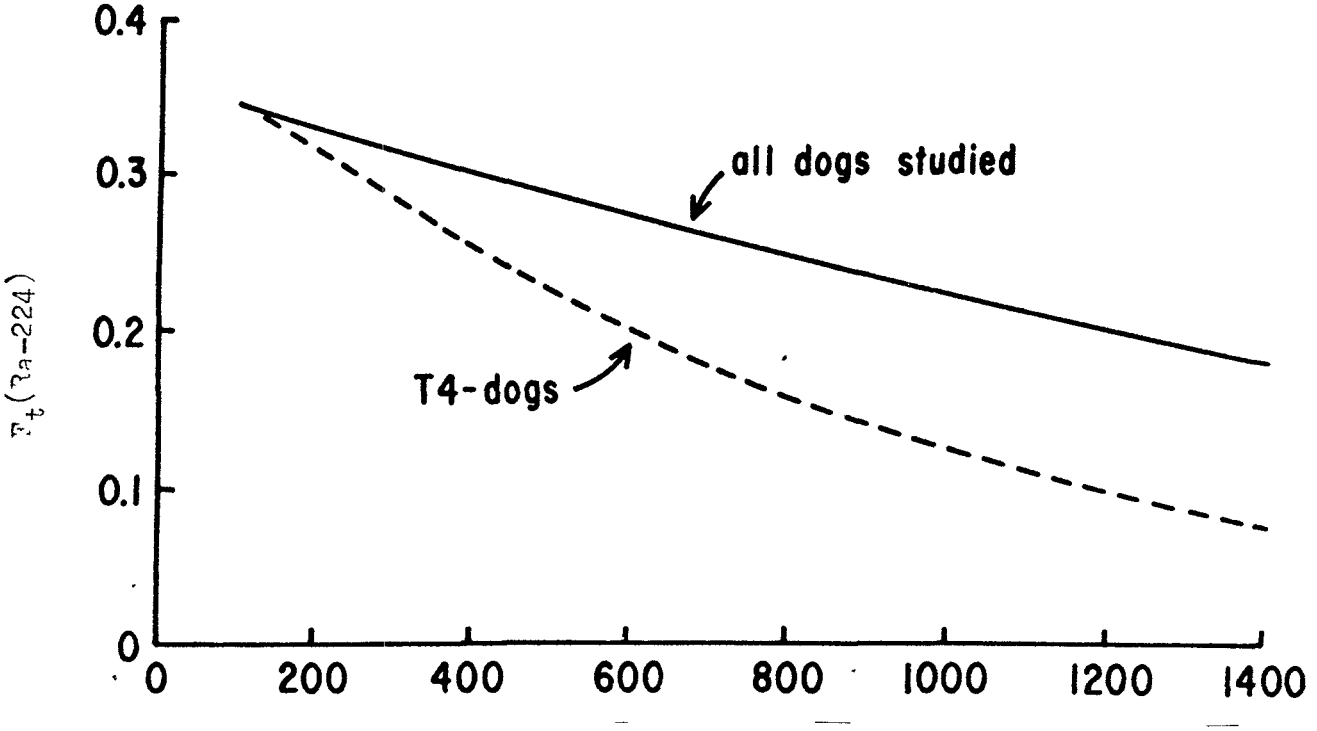


Fig. 2. Fraction of Ra-224 that translocates. At 20 - 30 days F_t(Ra-224) = 0.79

$$R(\text{Rn-220}) = 0.98\ R(\text{Ra-224}). \qquad (2)$$

The right hand side of Eq. (2) is given in Table 1. The dosimetric complication presented by Rn-220 is that present methods are not adequate to determine its distribution in the living animal. This is best discussed in conjunction with Pb-212.

The 10.6 hour half-period of Pb-212 permits its determination in tissues if counting is begun shortly after sacrifice of the animal (Stover et al., 1965). The results are summarized in Table 1. Fecal excretion is negligible, and while some Pb-212 formed in vivo is excreted in the urine, it does not significantly reduce the retention as shown in Table 1 (Stover et al., 1965; Stover, 1959).

When lead is injected into the blood in tracer amounts, a large fraction is associated with blood cells.* Mortensen (1944), using adult dogs and guinea pigs, showed that the fraction of Pb-210 in cells decreased as the amount of carrier lead increased. Schubert and White (1952) noted the same effect and determined a 30 hour biological half period for Pb-210 associated with rat blood cells. Hevesy and Nylin (1953) investigated the use of Pb-212 labeled blood cells for blood volume studies in humans. From their data a minimum value of 17 hours for the biological half period of Pb-212 associated with human blood cells was calculated (Stover, 1959). In young adult beagles the half-period was found to be 37 hours (Stover, 1959). Thus, tracer Pb-212 (and Pb-210) is found in association with blood cells in several mammalian species and the biological half period is significantly longer than the half period for radioactive decay. The rele-

* There are many reports in the literature of the association of tracer lead and blood cells in addition to those cited below.

vance of this to dosimetry of Th-228 is that Rn-220 and Po-216 are continuously decaying in the blood to form Pb-212 which in part becomes associated with blood cells. The result is a high steady-state concentration of Pb-212 in blood cells (see Table 1). From this concentration the fraction of Rn-220 and Po-216 that decays in the circulation can be estimated, if it is assumed that Pb-212 formed in the blood behaves as though it had been injected intravenously and that all Pb-212 in blood is formed there. The result of the calculation is as follows:

$$\text{Maximum \% Rn-220 decaying in blood} = 430C/0.52 = 9.1e^{-0.00097t}. \qquad (3)$$

The next member of the decay series, Bi-212, has a half-period of 60.5 minutes. Fecal excretion is negligible because of the short half-period. Although the activity of Bi-212 in a freshly voided urine sample exceeds those of Pb-212, Ra-224, and Th-228 by appreciable factors, the urinary excretion of Bi-212 does not significantly reduce its retention (see Table 1). This is a consequence of its short half-period. The plasma concentration of Bi-212 is roughly twice that of Ra-224, and of the Bi-212 formed from Pb-212 in or on blood cells 92 % decays there. In kidneys Bi-212 activity exceeds that of Pb-212. From 0.5 to 2 % Bi-212 moves to kidneys and urine from other but unknown sites within the dog (Stover et al., 1965; Stover et al., 1965a). Following the branched decay of Bi-212 are Po-212 and Tl-208 which have 0.3 μsec and 3.1 minute half-periods, respectively. These are too short for measurements of this kind.

5. Estimates of average radiation dose rates

The results given in Table 1 and the preceding section can be used to estimate average radiation dose rates to bone, liver, and kidneys (Stover et al., 1965). The skeletal retentions of Th-228, Ra-224, and Pb-212 have been determined. The activities of Bi-212, Po-212, and Tl-208 in the skeleton are assumed equal to that of Pb-212. (Even if the 0.5 to 2 % Bi-212 that moves to kidneys and urine comes from bone, the effect on the calculation is negligible.) The skeletal retentions of Rn-220 and Po-212 can be bracketed. If all Rn-220 that is exhaled or decays in the blood comes from soft tissues then skeletal Rn-220 activity equals that of Ra-224. This establishes the upper limit. The lower limit is set by assuming that all the Rn-220 exhaled and decaying in the blood comes from the skeleton. From B(Ra-224) of Table 1, Eq. (3), and the estimate of Rn-220 exhalation = $2.5e^{-0.0003t}$ (Stover et al., 1965a), the limits are as follows:

$$B_{max}(\text{Rn-220}) = 62e^{-0.00014t} \qquad (4)$$

$$B_{min}(\text{Rn-220}) = 62e^{-0.00014t} - 9.1e^{-0.00097t} - 2.5e^{-0.0003t}. \qquad (5)$$

The actual Rn-220 skeletal activity is between these two values, but very probably it is close to the maximum, Eq. (4). From Table 1 it is seen that the rates of decrease of Ra-224 in liver and spleen are about the same as that for Pb-212 in blood cells, but the rate of decrease of Ra-224 in bone is much slower. This similarity in rates indicates that soft tissues are the main source of exhaled and blood Rn-220. Actually the minimal and maximal average skeletal dose rates do not differ greatly. They are given by the following equations:

$$\frac{dD_{max}}{dt} = 10.6e^{-0.00114t} \text{ I rads/day} \quad (6)$$

and

$$\frac{dD_{min}}{dt} = 10.6e^{-0.00114t} - 0.62e^{-0.00197t} - 0.17e^{-0.0013t} \text{ I rads/day} \quad (7)$$

where I = μCi Th-228 injected/kg.

The difference between Eqs. (6) and (7) is small. The important question is which sites receive the energy from the nuclides that decay in the blood. Since they are not known, only the rate of energy dissipation can be calculated. The maximum rate of energy release from Rn-220 and Po-216 decay in the blood is

$$\simeq 6200IWe^{-0.00197t} \text{ ergs/day} \quad (8)$$

and the energy release rate from Pb-212 and decay products associated with blood cells is

$$1950IWe^{-0.00197t} \text{ ergs/day} \quad (9)$$

where W = weight in kg. Some of this energy must be dissipated in capillary walls with consequent vascular damage.

The limits on average radiation dose rates to the liver calculated using equations from Table 1 and complete and zero retentions of Rn-220 and Po-216 in the liver are given by the following:

$$\frac{dD_{max}}{dt} = 2.32Ie^{-0.0020t} \text{ rads/day} \quad (10)$$

$$\frac{dD_{min}}{dt} = 1.37Ie^{-0.0020t} \text{ rads/day} . \quad (11)$$

There was greater variation in dose rates to the kidneys. The maximum and minimum values ranged from 0.24IW and 0.21IW rads/day at 65 days to 0.057IW and 0.043IW rads/day at 833 days.

6. Summary

(1) The distribution of thorium depends on the amount introduced into the blood. Tracer amounts deposit principally on bone surfaces with small amounts going to the RE cells and the kidneys. As the amount increases the pattern shifts so that liver and then bone marrow become the principal deposition sites. It is not known whether the formation of the colloidal thorium occurs in the blood of the animal or during the course of preparation of the injection solution, or both.

(2) After injection of Th-228 some of the Rn-220, Pb-212, and Bi-212 that is formed in vivo is excreted. However, the excretion is not sufficient to effect a substantial reduction in radiation dose rate.

(3) Quantitative information for the calculation of average radiation dose rates to selected tissues has been obtained for Ra-224 and Pb-212. Qualitative information on the microdistribution of Ra-224 can be obtained autoradiographically.

(4) It has been shown that Rn-220 and Bi-212 move within the animal but it is not possible with existing methods to do quantitative distribution studies. The amount of Rn-220 that decays in blood has been estimated, and Bi-212 in kidneys has been measured.

METABOLISM OF Ra-224 AND DESCENDANTS AFTER INJECTION INTO BLOOD OF HUMANS

L. Kosta and P. Horvat

1. Introduction

The metabolic behavior of radium at long times after intake into humans appears to be well established in an abundant literature. Recent work reflects an increasing interest in its pattern of distribution and elimination in the first days after intake. For such studies Ra-224 is especially suitable. The high activities which may be administered because of its short half life permit the attainment of reliable data both for radium itself and for its three decay products Rn-220, Pb-212, and Bi-212. Since these radionuclides have a major influence on the dose distribution in patients with incorporated Thorotrast, studies on Ra-224 are directly related to the toxicology not only of radium but also of Thorotrast. The fact that Ra-224 is actually in use for treatment of certain diseases such as spondylarthrosis ankylopoietica (Bechterew's disease) allows measurements to be made on patients without subjecting them to irradiation for the sake of experimentation alone.

The most extensive work on the behavior of Ra-224 was done by Koch (1957). He was primarily concerned with the effects of α-rays on bone growth, and based his study mainly on autoradiographic measurements. However, he also included measurements on β-ray and γ-ray activity in excreta, and obtained data on the fecal excretion of Ra-224 which are essentially in agreement with recent data. In addition, from the analysis of decay curves he pointed out differences in the distribution of Ra-224 and Pb-212 in blood and various organs. Schales (1964) reported new results, based mainly on γ-ray spectrometry, on three patients who received therapeutic injections of Ra-224. His measurements concern changes in body burden with time and include quantitative data on the elimination of Ra-224 in excreta (although for feces they seem to be too low). In addition he investigated Rn-220 (thoron) exhalation and presented a curve showing its elimination with time. Regarding the equilibrium status between Ra-224 and its decay products he found relative to Ra-224 an excess of Pb-212 and Bi-212 in urine, and Pb-212 in red blood cells.

Our own measurements were conducted on patients receiving 32 μCi of Ra-224 as treatment for Bechterew's disease at the Orthopedic Clinic in Ljubljana. Their purpose was to clarify the radiation dose situation in Ra-224 therapy. Although radium tends to concentrate in areas of active bone reconstruction, most is excreted before deposition takes place. As a result, other organs are also irradiated. Furthermore, we are dealing with a radioactive chain in which the parent nuclide, Ra-224, contributes only 24% of the total α-ray energy. Therefore the dose to particular organs may vary within wide limits according to the behavior of individual decay products.

Data on the distribution, concentration and elimination of the Ra-224 series nuclides were obtained for blood, urine, and feces by taking samples at certain intervals and measuring the subsequent time-course of the γ-ray activity until it reached equilibrium. To obtain a general picture, measurements were made on groups, rather than on individual patients as was usually the case in earlier studies. The distribution of γ-ray emitting activity in the body was measured in 8 patients, blood samples were taken from 9, and urine from 6. Data on the excretion of Ra-224 through urine and feces were obtained from 2 patients who were hospitalized to make quantitative collection of excreta possible.

One experiment was also performed on a rat, which was injected intravenously with 15 μCi Ra-224 in equilibrium with its daughter products. The β-ray and γ-ray activities of the whole animal were measured under conditions of high geometrical efficiency and compared against an aliquot of the injection solution. Urine and feces were collected and measured separately during a period of 8 days, at which time the animal was sacrificed and the distribution and equilibrium status of the Ra-224 in the various organs determined.

2. Excretion of Ra-224

Most of the Ra-224 is excreted in the feces soon after injection: about 50% by 1-2 days, 50-70% by 5 days. In the urine 1-4% is excreted, the majority during the first day. The rate of excretion is low after 5 days, in conformity with the observations of others (Schales, 1964; Looney et al, 1955; Marinelli et al, 1953). By this time the residual Ra-224 must be mainly deposited in organs with slow metabolism. There are differences in the shapes of excretion curves, depending on the frequency and quantity of excretion from individual patients. An oral administration might have shown even more pronounced variability, as indicated in experiments by Muth (1954) in dogs.

Contrary to data published earlier (Scheer, 1950), our rat behaved similarly to humans: at 5 days cumulative excretion amounted to 70% in feces and 3% in urine.

3. Ra-224, Pb-212, and Bi-212 in blood

By analyzing the growth and decay of the γ-ray emitters in blood samples it is possible to deduce the Ra-224, Pb-212, and to some extent Bi-212 concentrations at the moment of sampling. The concentration of Ra-224 in blood in vivo decreases very rapidly to 10% of its initial value at one hour and <1% at 6 hours. The concentration of Pb-212, on the other hand, increases during the first 10 hours, but later diminishes for several days with an effective half life of about 30 hours. This high value (about 3 times the physical half life of Pb-212) reflects the continuing replenishment of Pb-212 by decay in the blood of Rn-220 newly formed from Ra-224 in the body.

Ra-224 and Pb-212 also behave quite differently with respect to their distribution in the blood. The high affinity of lead for red blood cells is known from toxicological investigations on chronic lead poisoning, and observations on Ra-224 and Pb-212 themselves have already been reported by other authors. Our measurements have shown a practically quantitative separation of these nuclides, with Ra-224 in the plasma and Pb-212 in the red cells as early as one half hour after injection.

At the moment of blood withdrawal Bi-212 is at a lower activity than Pb-212, indicating that it is partially eliminated from the blood stream.

4. Rn-220 in breath

As a consequence of the chemical inertness and high mobility of the rare gases, Rn-220 can be exhaled by the patient. However, its short half life (54 sec) restricts exhalation to a small percentage. Translocation as well as a variable rate of excretion of Ra-224 further complicate the picture and explain the shape of the curves obtained by Schales in exhalation measurements on Rn-220 in humans.

We observed Rn-220 exhalation from 2 patients. While the accuracy of our results is not high because of experimental difficulties, the Rn-220 we observed in the exhaled breath (expressed as a percent of that in equilibrium with the injected Ra-224) was as follows:

Time after injection (hours)	0.1	.1	24	72
% Rn-220 in breath	4.4	2.2	0.8	0.15

5. Pb-212 and Bi-212 in urine

At one half hour after injection, urine contains a high excess of Bi-212 over Pb-212. In 5 out of 6 patients the Pb-212 activity in the urine at this same time was about 1/3 to 1/2 the Ra-224 activity; in the sixth patient the urinary Pb-212 activity exceeded the Ra-224 activity.

6. Distribution of γ-ray emitters in body

The distribution of γ-ray emitters in the human body was studied using a collimated NaI(Tl) scintillation detector. In general there was a tendency for the counting rate over the forehead, knee, and upper vertebrae to increase during the first week relative to that over the stomach or lower vertebrae. The superposition of the activity in blood and soft tissue upon that in the bones made these comparisons difficult to interpret at early times with the simple equipment available.

In the rat sacrificed 8 days after injection we observed the following distribution of the retained Ra-224: bones, 89.5%, intestine, 1.6%; skin, 0.6%; lungs, 0.3%; liver, 0.1%. Pb-212 was above equilibrium in liver, kidneys, skin, and blood, and much below equilibrium (~ 25%) in bones.

Acknowledgments

This investigation was undertaken at the suggestion of Academician Prof. B. Brecelj, Head of the Orthopedic Clinic in Ljubljana, whom we thank for his interest and encouragement.

DOSE IN SKELETON AND BONE MARROW FOLLOWING THOROTRAST INJECTION INTO BLOOD

A. Kaul

1. Introduction

Our present knowledge of the radiation dose in the skeleton and bone marrow of Thorotrast patients is by no means as comprehensive as that of the dose in, for example, the liver and spleen, although even in these tissues many basic problems require further study. The reasons for this are mainly the following: (1) As 70 % or more of the injected Thorotrast is located in the liver and spleen (and possibly additional amounts in perivascular deposits), a direct measurement of the amount in the skeleton and bone marrow by whole-body counting is not possible. (2) The distribution of Th-232 and its daughter products in the skeleton may therefore be studied only by analyzing tissue samples of Thorotrast patients after death; however, the total number of such cases published in the literature is extremely small. (3) In some of these cases considerable time elapsed between autopsy and analysis, so that little or no information on the short-lived Th-232 daughters at the time of autopsy is available. (4) In all cases the activity of the entire skeleton and that of the bone marrow has been estimated by extrapolating the results of measurements on small specimens to the entire skeleton. This procedure, although unavoidable, is not accurate.

2. Th-232 content of skeleton and bone marrow

In a careful study Marinelli and Lucas (1962, 1963) have compiled the data available in the literature concerning total skeletal activity of Th-232 (as % of injected Th-232) in samples of fresh trabecular bone containing marrow and in samples of marrow-free trabecular and cortical bone. The values were obtained by extrapolating the activity of a given specimen to the whole skeleton by assuming a weight of 7000 g for the skeleton and 2800 g for its ash, and by dividing this value by the activity of the Thorotrast injected. These data, supplemented by our own results (Kaul, 1965; Kaul and Rajewsky, 1966), are given in Tables 1 and 2. The results indicate that about 30 % of the Th-232 injected into blood is deposited in marrow, and 0.6 % in marrow-free bone. Though not very numerous the results agree rather well despite the variety of methods employed by the different authors.

3. Steady-state activity ratios in vivo

Data on the activity ratios Th-228/Th-232 and Th-228/Ra-228 in bone with and without marrow are collected in Tables 3 - 6. They are taken from Marinelli and Lucas (1962, 1963) with additions from our own results. The ratio Th-228/Th-232 is about 0.2 in marrow, about 1.7 in marrow-free bone. A wide range of values for the ratio Th-228/Ra-228 has been reported for bone with marrow, but a mean value near unity appears to be suggested. In marrow-free trabecular or cortical bone this ratio is about 1.10, suggesting only a small translocation of Th-228

TABLE 1

Total skeletal Th-232 (% of injected Th-232) as obtained from extrapolation of measurements of trabecular bone containing marrow

Specimen	Thorotrast injected (ml)	Method of analysis	Total skeletal Th-232 act. as % of injected Th-232	Author
Cancellous bone	75	Spectrochemical	6.0	Hursh et al.(1957)
Cancellous bone	75	Spectrochemical	24.6	Hursh et al. (1957)
Sternum bone	60	Radiochemical	34.	Turner et al. (1958)
Rib	50	Radiochemical α-spectrometry	32.7	Marinelli and Lucas (1963)
Sternum Rib Vertebrae	~ 40	α-coincidence	32. *	Kaul and Rajewsky (1966) Kaul (1965)
Bodies of vertebrae, sternum, iliac crest	~ 40	α-coincidence	31. *	Ditto

* Average values obtained from different bone samples of one patient

TABLE 2

Total skeletal Th-232 (% of injected Th-232) as obtained from extrapolation of measurements of clean trabecular or cortical bone

Specimen	Thorotrast injected (ml)	Method of analysis	Total skeletal Th-232 act. as % of injected Th-232	Author
Molar tooth	10	Radiochemical α-spectrometry	0.50	Marinelli and Stehney (1957)
Compact bone	75	Spectrochemical	0.56	Hursh et al. (1957)
Compact bone	75	Spectrochemical	0.56	Hursh et al. (1957)
Trabec. tibia	10	Radiochemical α-spectrometry	0.82	Marinelli and Lucas (1962, 1963)
Trabec. femur			0.77	
Cortical femur			0.4	
Cortical tibia			0.46	
Cortical femur	50	Radiochemical α-spectrometry	0.44	Marinelli and Lucas (1963)
Cortical femur	~ 40	α-coincidence	0.8 *	Kaul and Rajewsky (1966) Kaul (1965)

* Average values obtained from different bone samples of one patient

TABLE 3

Activity ratio Th-228/Th-232 in samples of bone marrow and fresh trabecular bone containing marrow

Specimen	Thorotrast injected (ml)	Method of analysis	Activity ratio Th-228/Th-232	Author
Sternum	60	Radiochemical	0.17	Turner et al. (1958)
Rib	50	Radiochemical α-spectrometry	0.10	Marinelli and Lucas (1963)
Bone marrow	~ 40	α-coincidence	0.21	Kaul (1965)
Bone marrow	~ 40	α-coincidence	0.36	Stahlhofen and Kaul (1964)
Bone marrow	~ 40	α-coincidence	0.23	Unnewehr et al. (1964)

TABLE 4

Activity ratio Th-228/Th-232 in samples of trabecular or cortical bone without marrow

Specimen	Thorotrast injected (ml)	Method of analysis	Activity ratio Th-228/Th-232	Author
Molar tooth	10	Radiochemical α-spectrometry	3.40	Marinelli and Stehney (1957)
Trabec. tibia	10	Radiochemical α-spectrometry	1.45	Marinelli and Lucas (1962, 1963)
Trabec. femur			1.52	
Cortical femur			1.80	
Cortical femur			1.88	
Cortical tibia			1.61	
Cortical femur	50	Radiochemical α-spectrometry	2.04	Marinelli and Lucas (1963)
Rib (inorganic)			0.61	
Cortical femur	~ 40	α-coincidence	2.00	Kaul (1965) Stahlhofen and Kaul (1964) Unnewehr et al. (1964)
Cortical femur			1.67	
Vertebra	~ 40		1.43	
Vertebra			1.43	
Sternum			1.67	
Rib			2.00	

TABLE 5

Activity ratio Th-228/Ra-228 in samples of bone marrow and fresh trabecular bone containing marrow

Specimen	Thorotrast injected (ml)	Method of analysis	Activity ratio Th-228/Ra-228	Author
Body of vertebra	20	Radiochemical	1.12	Turner et al. (1958)
Head of femur			0.90	
Sternum	60	Radiochemical	0.88	Turner et al. (1958)
Sternum			1.17	
Rib	50	Radiochemical α-spectrometry	0.30	Marinelli and Lucas (1963)
Bone marrow	~ 40	γ-spectrometry	1.11	Kaul (1965)
Bone marrow			1.18	
Bone marrow	~ 40		1.08	

TABLE 6

Activity ratio Th-228/Ra-228 in samples of bone without marrow

Specimen	Thorotrast injected (ml)	Method of analysis	Activity ratio Th-228/Ra-228	Author
Vertebral bone	(75)	Radiochemical	0.76	Marinelli and Lucas (1962, 1963)
Trabec. tibia	10	Radiochemical α-spectrometry	1.03	Marinelli and Lucas (1962, 1963)
Trabec. femur			1.52	
Cortical femur			1.14	
Cortical femur			1.19	
Cortical tibia			0.79	
Cortical femur	50	γ-spectrometry	1.20	Marinelli and Lucas (1962, 1963)
Cortical femur			1.48	
Cortical femur			1.02	
Vertebrae*			0.66	
Rib (inorganic)			0.61	
Cortical femur	~ 40	γ-spectrometry	1.67	Kaul (1965) Stahlhofen and Kaul (1964)
Vertebra			1.09	
Vertebra			1.18	
Iliac crest			1.11	
Sternum			1.27	
Vertebra	~ 40		1.11	
Sternum			1.12	

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

itself to the skeleton. The excess of Th-228 relative to Th-232 in marrow-free bone is to be attributed to transfer of its parent, Ra-228, to the skeleton, and retention therein of the subsequently produced Th-228.

The ratio Ra-224/Th-228 appears to have been measured in the skeleton of only one subject, a person whose complete femur we obtained 30 hours after death (Kaul and Rajewsky, 1966). Samples of compact bone (diaphysis) mechanically cleaned of soft tissue, spongiosa, and marrow, and samples of spongiosa and bone marrow themselves, were analysed by γ-ray spectrometry at frequent intervals during the next few days. In all samples Ra-224 appeared to be within ± 10 % of equilibrium with Th-228. It also seems probable that Rn-220 and Pb-212 are not released from the skeleton to an important extent.

4. Ra-228, Th-228, and Ra-224 contents of skeleton

Information on the distribution of Th-232, Ra-228, and Th-228 in liver and spleen, skeleton with marrow, and skeleton without marrow is collected in Table 7. These figures have been calculated from the average activity ratio data in Tables 4 and 6, and Th-232 distribution data summarized by the author previously at this meeting. Our own analyses have shown 16 % and 19 % of the body's Ra-228 and Th-228, respectively, to be in skeleton with marrow, while 2 % and 3 %, respectively, were in marrow-free skeleton. If Ra-224 is at equilibrium with Th-228 in the skeleton, as suggested in Section 2, and if for the total body the activities of Ra-224 and Th-232 are in the ratio 0.38 (Kaul, this meeting), then about 3.2 % of the body's total Ra-224 is in the marrow-free skeleton.

TABLE 7

Average distribution of Th-232, Ra-228, and Th-228 in the bodies of patients after injection of Thorotrast into blood (calculated from measured values)

	Liver, Spleen		Skeleton			
			With marrow		Free of marrow	
Nuclide	Act. ratio	% of total body content	Act. ratio	% of total body content	Act. ratio	% of total body content
Th-232	1.00	69	1.00	30	1.00	0.6
Ra-228	0.50	82.6	0.22	15.6	1.58	2.3
Th-228	0.45	80.6	0.21	16.6	1.75	2.8

4. Radiation dose in skeleton and bone marrow

Calculations of the dose in skeleton and bone marrow have been made, using the author's own results on the distribution of the Th-232 decay series nuclides in the body after injection of Thorotrast into the blood. The following additional assumptions were made: (1) at injection the activity ratios were Th-228/Th-232 = 1.00, Ra-228/Th-232 = 0.00; (2) Th-232 is present in the skeleton at a constant amount from the moment of injection, namely 0.8 % in bone and 30 % in marrow (average values in literature: 0.6 % and 26 % many years post injection); (3) Th-228 activity in the skeleton and bone marrow is initially identical to that of Th-232; (4) Ra-228 and Th-228 translocate into the marrow-free skeleton from the reticulo-endothelial system at a rate proportional to the amounts present in the RES, such that at 20 years 2 % and 3 % of the respective body burdens are found in the sksleton; (5) absorption of the α-particle energy in the ThO_2 agglomerates themselves is negligible (an assumption leading, especially in bone marrow, to an overestimate of dose).

Assumptions (2) and (3) may be inaccurate, but more exact information is unavailable. Rundo and Hjort (1953) showed that some Th-232 is indeed present in the skeleton. In an autoradiograph of a rabbit femur a grain of thorium-containing material was observed in a Volkmann canal. This was not contained in a cell, and the authors advanced a suggestion of Barkan and Kienast (1935) to explain its presence: thorium-containing material probably escapes from cells upon their death and may be transported to another organ via the bloodstream.

Table 8 shows the dose rates and cumulative dose (about 95 % from α rays, 5 % from β rays) as of 20 years after injection of 20 ml Thorotrast into the blood. For comparison, corresponding figures are also listed for a constant magnitude of 0.1 μCi Ra-226 in the skeleton (the maximum permissible burden). Marinelli (1957) estimated the skeletal dose rate from Thorotrast to be somewhat higher (40 % - 100 % of that associated with 0.1 μCi Ra-226). Hursh et al. (1957) estimated a dose rate in marrow about 1/4 of ours, while Rundo (1958) estimated a value of about half ours (assuming 10 % of body's Th-232 in marrow).

TABLE 8

Skeletal dose rates and cumulative doses at 20 years

Site	Thorotrast		0.1 μCi Ra-226	
	mrad/week	rad	mrad/week	rad
5 μm osteocyte	10	25	70	80
trabecular bone marrow	220	220	5	5

To date no bone lesions have been described which could be attributed to Thorotrast (Looney, 1960; Faber, 1962). Since injections of 100 ml Thorotrast were not too uncommon in diagnostic radiography, our

DOSES TO LUNGS FROM BREATH THORON AND PRIMARY THOROTRAST DEPOSITS

H. Muth and R. Grillmaier

1. Introduction

The radiation dose to the lungs of Thorotrast patients has two origins. First, part of the thoron (Rn-220, or Tn) escapes from the primary deposits and enters the lung. A fraction decays there and contributes, along with its decay products, one component of the dose. Second, some of the colloidal Thorotrast is itself deposited in the lung and irradiates it thereafter. In this paper we review present knowledge concerning both of these radiation sources.

2. Doses from thoron

2.1. Results of other workers

Stenstrom (1941) was apparently the first to demonstrate Tn in the breath of a Thorotrast case, but he did not quantify the observations.

Rundo et al. (1958) reported quantitative measurements on about 200 cases. The seated patient exhaled strongly through a drying column into a plastic bag, "4 - 6 deep breaths being collected for exactly 30 seconds". Four liters of the breath were then drawn into an ionization chamber. About half of the 200 cases were injected with known volumes of Thorotrast, and for these the authors deduced (under certain assumptions about the equilibrium status of the Th-232 decay series during the interval since injection) that about 3×10^{-3} μCi Tn is found per liter of breath for each μCi of Th-228 in the body. This figure implies that about 8 % of the Tn produced in the liver and spleen is exhaled.

From these data the same authors then calculated the average radiation dose rates to the entire lung, assuming further that: (1) the concentration of Tn in the 3 liters of air in the lungs is the same as that in the breath, (2) blood Tn can be neglected, and (3) the lungs weigh 800 g. The result was that per ml of Thorotrast injected the dose rate is 0.8 mrad/week at 5 years after injection, or 1.9 mrad/week at 30 years. Thus for an injected volume of 20 ml (common in cerebral angiography) typical dose rates are 16 - 37 mrad/week, and for 75 ml injected (common in hepatosplenography), 59 - 140 mrad/week. If a quality factor of 10 is used in the interpretation of these α-ray doses, the rem rates equal or exceed the maximum permissible level for occupational exposure.

Finally, Rundo and colleagues pointed out that the doses delivered to the epithelium of the bronchus and trachea must be much higher than the lung average. In these large air passages the volume of air per gram of irradiated tissue (to a depth of about 50 μ) is much greater than the lung average. Nevertheless, it is uncertain whether the Tn daughter products in these regions are elevated in proportion to the Tn. According to Chamberlain and Dyson (1956), the Pb-212 deposited on the

calculations would suggest that doses α of 120 rad (corresponding, assuming a quality factor of 10, to 1200 rem) delivered to the skeleton in 20 years is insufficient to induce bone lesions. From a comprehensive study of the literature, Langendorff and Kriegel (1963) suggested that at least 1500 rem was necessary to induce a bone tumor in man.

According to Looney (1960) no specific type of leukemia has yet been found in Thorotrast cases. Since to date only 10 cases of leukemia have been reported in Thorotrast patients (Faber, 1962) we cannot be sure that Thorotrast induces leukemia. Nevertheless, injection of 50 ml of Thorotrast would deliver to the marrow in 15 years 450 rad or 4500 rem.

walls of the bronchus should be moved with the mucus out of the bronchial tubes and probably also out of the trachea before decaying; on the other hand, this Pb-212 will be replaced at least in part by Pb-212 transported with the mucus from deeper within the lung. For a bronchus of radius 0.6 cm Rundo and coworkers calculated the following dose rates at 30 years after injection of 1 ml Thorotrast: 18 mrad/week if only Tn and Po-216 decay in the bronchus, 30 mrad/week if the rest of the chain also decays there. These values are 10 - 15 times the lung average and in rem units exceed the maximum permissible values. After an injection of 75 ml Thorotrast, the cumulative dose in the bronchus during the next 16 years is 720 - 1155 rad.

2.2. Results from our investigations

Grillmaier (1964) measured the Tn concentration in the exhaled breath of 45 Thorotrast cases. About half had deposits mainly in the reticulo-endothelial system; the other half had deposits mainly perivascularly. The equipment used for these measurements and its calibration are described elsewhere (Grillmaier et al., 1964a, 1964b). The lowest detectable Tn concentration is 1.6×10^{-11} Ci/l. The main features of this equipment are: (1) collection of breath under physiological conditions, (2) determination of breathing rate during breath collection, (3) measurement of Tn concentration during longer breath collection period (10 - 15 min), (4) analysis of decay curves not required.

The chief results of these measurements were: (1) The percentage exhalation of Tn is 8 % ± 3 % for deposits mainly in RES, 4 % ± 1 % for perivascular deposits. (2) The Tn concentration in the breath of Thorotrast cases is in the range $0.2 - 6.0 \times 10^{-9}$ Ci/l, and averages 8.1×10^{-9} Ci/l for 1 µCi Th-228 in a case with an RES deposit. This latter figure is about twice as large as that reported by Rundo et al. (1958). The discrepancy may be attributable to the non-physiological breath sampling technique of these workers.

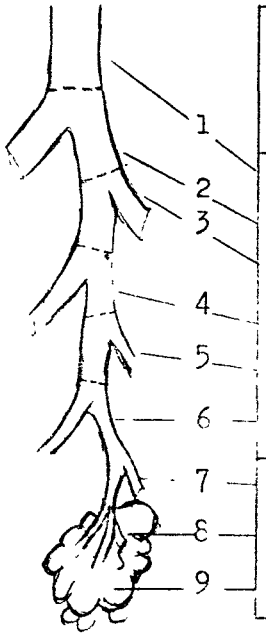
From our results on Tn exhalation we have made our own estimate of α-ray dose rates to the lung. The amount of Tn decaying in the lung cannot be measured directly. We have used two different indirect methods to evaluate this quantity, of which the simplest and most accurate is here summarized. We assume the following parameters: breath volume = 0.5 liter, lung volume = 3.25 liter, and breathing rate = 7.0 liter/min. These figures yield the mean residence time of the air and thereby of the Tn in the lungs. From the mean residence time and the fraction of Tn exhaled, the fraction of Tn decaying in the lungs is calculated. For persons with RES deposits, one deduces that 3.1 % of the Tn formed in the body decays in the lungs; for those with perivascular deposits the result is 1.6 %.

In calculating the amount of Tn formed in the body as a function of time after Thorotrast administration, we have assumed that no Ra-228 is injected, that initial Th-228 and Th-232 activities are equal, and that 50 % of the Ra-228 formed in vivo is excreted. In evaluating the activity ratios of the daughter products in the lungs we must consider the following issues: the rate of deposition of Tn daughters on lung epithelium, the rate of attachment of Tn daughters to aerosol particles

in the air, the rate of transfer of the radioactive atoms (whether still in air or on epithelium) out of different parts of the lungs, and the dimensions of different regions of the lungs. Concerning the last we use the model of the lung (Table 1) given by Landahl (1950, 1963). (See also Jacobi, 1964 and Altshuler et al., 1964.) The situation with respect to these issues is different in different regions of the lung, which we therefore consider separately.

TABLE 1

Anatomic model of human lung



Region	Number	Diameter (cm)	Length (cm)	Total Surface Area (cm^2)	Total Volume (cm^3)	Ciliary Transport Velocity (cm/min)
Trachea	1	1.6	12	60	24	1.5
Main Br.	2	1.0	6	40	10	0.8
Lobar Br.	12	0.4	3	45	5	0.3
Segm. Br.	100	0.2	1.5	100	5	0.1
Subseg. Br.	800	0.15	0.5	200	10	0.02
Terminal Br.	6×10^4	0.06	0.3	3400	50	0.004
Resp. Br.	2×10^5	0.05	0.15	4700	60	-
Alveol.Duct.	5×10^6	0.04	0.05	30000	300	-
Alveol.Sacc.	5×10^7	0.04		250000	2500	-

Region of alveoli. Practically all atoms of Po-216 or Pb-212 formed within the alveoli are deposited as free atoms on their walls, as the following argument shows. We assume the alveoli to be spheres having the dimensions given in Table 1. The concentration c of these atoms depends on the distance from the center of the sphere. In a small concentric shell of thickness Δr, in the steady state, the sum of the number of free atoms entering the shell across its inner surface and the number of atoms formed by decay of Tn within the shell must be equal to the sum of the number of atoms leaving the shell by its outer surface and the number of atoms lost within it by attachment to aerosol particles and by decay:

$$-4\pi r^2 \frac{dc}{dr}\Big|_r + \lambda_6 \frac{n_6}{V} 4\pi r^2 \Delta r = -4\pi (r + \Delta r)^2 D \frac{dc}{dr}\Big|_{r+\Delta r} + 4\pi r^2 \lambda_i c \Delta r + 4\pi r^2 \lambda' c \Delta r$$

$\lambda_6 \equiv$ physical decay constant of Tn
$n_6 \equiv$ number of Tn atoms in lung
$V \equiv$ volume of lung
$D \equiv$ diffusion coefficient

$\lambda_i \equiv$ physical decay constant of Tn daughter product in consideration
$\lambda' \equiv$ fraction of number of free atoms which attach to aerosol particles per unit time

For $\Delta r \to o$ we have:

$$\frac{d^2c}{dr^2} + \frac{2}{r}\frac{dc}{dr} - \frac{\lambda_i + \lambda'}{D} c + \frac{\lambda_\ell n_\ell}{DV} = o$$

Let z = number of free atoms being deposited on the wall of the alveolus (radius = a) per unit time. Then

$$z = 9\lambda_\ell n_\ell \frac{D}{(\lambda_i+\lambda')a^3}\left[a\sqrt{\frac{\lambda_i+\lambda'}{D}}\coth\left(\sqrt{\frac{\lambda_i+\lambda'}{D}}\cdot a\right)-1\right].$$

With a = 0.02 cm, D = 0.05 cm^2/sec (Chamberlain and Dyson, 1956), and $\lambda' = 0.0115\ sec^{-1}$ (Jacobi 1961, 1963, 1964) we find for Po-216 $z = 0.96\lambda_\ell n_\ell$ and for Pb-212 $z = \lambda_\ell n_\ell$, i.e., almost the same as the rate of formation of these atoms in the alveoli.

The activity of the Tn decay products on the alveoli epithelium then depends on the rate of their removal from the alveoli. Aurand et al. (1955) suggest that aerosol particles deposited in the alveoli are removed with a half life of 8 hours, 50 % progressing to the bronchial tree and 50 % being resorbed. Therefore Po-216 ($T_1/2$ = 0.16 sec) must be in radioactive equilibrium with Tn in the alveoli, while Pb-212 ($T_1/2$ = 10.6 hr) would be at 40 % of equilibrium if it were cleaned out at the same rate as the aerosol particles. However, the free Pb-212 atoms or ions probably combine with lung tissue (in which even stable Pb may be found in amounts up to 20 mg/100 g fresh tissue - Stewart and Stolmann (1960)) and remain there until decay. We conclude, therefore, that in the alveoli equilibrium exists between Tn and all its decay products.

Region of alveolar ducts and respiratory bronchi. Since the dimensions of these regions are similar to the dimensions of the alveoli, we assume that in these regions the same analysis applies and therefore that the Tn and all its decay products are in equilibrium.

Doses in total respiratory zone. We assume that all the α-ray energy from Tn and its equilibrated decay series is absorbed in the 800 g of lung tissue constituting the respiratory zone. This is only an approximation, since the membrane between air and blood is in places sufficiently thin that some unknown fraction of the α-ray energy is dissipated in blood rather than in lung tissue. On the other hand, the blood itself contains Pb-212, and we estimate from its concentration and the blood volume of the lung that about 1.8 % of the Pb-212 in the body (for subjects with RES deposits) is located in the blood in the lung. Here again we do not know how the α-ray energy deposition is divided between blood and lung tissue. However, probably the dose to lung from Pb-212 and descendants in the blood is less than 20 % - 35 % of the dose from Tn and decay products in the alveolar region. We henceforth ignore these difficulties in the expectation that the required lung-blood corrections are either small or approximately compensating. On the basis of these

assumptions, dose rates and accumulated doses as a function of time after injection of 45 ml Thorotrast are calculated as shown in Figs. 1 and 2 for subjects with RES deposits. For subjects with perivascular deposits the figures would be about half as large.

Region of bronchial tree and trachea. When estimating the activity ratios of Tn and its decay products in this region, we must take account of the translocation of substances deposited on the mucus layer by ciliary transport. It turns out, as shown below, that virtually none of the deposited Po-216 but virtually all of the Pb-212 is removed from this region by ciliary action.

We assume the different branches of the bronchial tree (Table 1) to be cylinders of different radii, and use the following symbols:

- $u \equiv$ velocity of ciliary transport in these branches
- $f \equiv$ number of atoms of the radionuclide concerned per unit area of the cylinder wall
- $n_\ell \equiv$ number of Tn atoms in the entire cylinder
- $c \equiv$ Tn disintegration rate per unit volume of air
- $V \equiv$ volume of the cylinder
- $h \equiv$ length of the cylinder
- $r \equiv$ radius of the cylinder
- $A_i \equiv$ total activity of the decay product concerned on the mucus layer of the cylinder wall

In the steady state the following conditions must be fulfilled for the element of surface area $2\pi r \cdot \Delta h$: The sum of the number of atoms transported from the lower regions of the bronchial tree into the surface element and the number deposited on the surface element from Tn decay in the air must equal the sum of the number of atoms transported away from this surface and the number decaying there:

$$2\pi ruf\Big|_h + \pi r^2 \Delta h c = 2\pi ruf\Big|_{h+\Delta h} + 2\pi r \Delta h \lambda_i f \ .$$

For $\Delta h \to 0$

$$\frac{df}{dh} + \frac{\lambda_i}{u} f - \frac{rc}{2u} = 0 \ .$$

The solution of this equation is

$$A_i = 2\pi rh \lambda_i f = \lambda_\ell n_\ell \left(1 - e^{-\frac{\lambda_i}{u} h}\right) .$$

Taking the data for the cylinder dimensions from Table 1 we get the following results:

For Po-216:	terminal bronchi (min u):	$A_7 = \lambda_6 n_6$
	trachea (max u) :	$A_7 = \lambda_6 n_6$
For Pb-212:	terminal bronchi:	$A_8 = 0.08\ \lambda_6 n_6$
	trachea	$A_8 < 0.01\ \lambda_6 n_6$

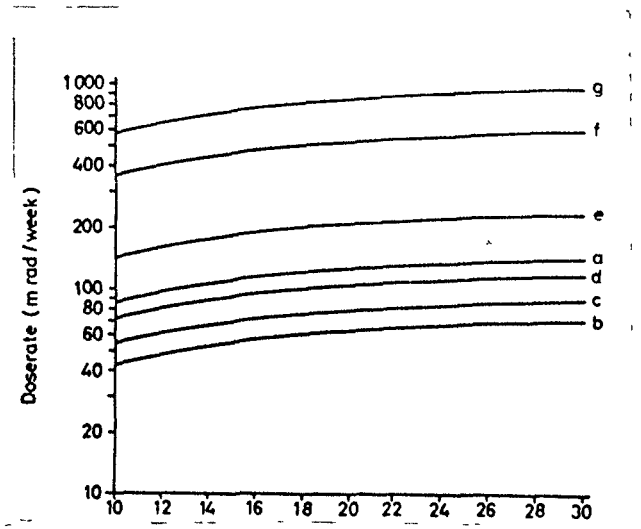
Therefore in bronchi and trachea we find the following conditions. During exhalation, Tn-laden air is in the passages; no Po-216 or Pb-212

are transported into these passages from below; Po-216 builds up on the walls to equilibrium with Tn in the air, but Pb-212 activity on the walls is negligible. During inhalation, the Tn-laden air is sucked back into the alveoli and fresh air fills the trachea and large bronchi. We assume that mixing of Tn-laden and Tn-free air occurs at a negligible rate in trachea and large bronchi because of their dimensions, but in the terminal bronchi (adjacent to the respiratory zone) mixing is complete. Hence the trachea and large bronchi are irradiated only half the time, while the terminal bronchi like the respiratory zone are irradiated continuously. In calculating the dose we have assumed that the α-rays penetrate a depth of 0.005 cm in unit density tissue. We have ignored the deposition of α-ray energy in the mucous layer itself, which ranges in thickness from 10^{-4} cm in the lower regions to 10^{-3} cm in the trachea. Therefore the calculated doses are possibley too high by as much as 20 %. The results are included in Figs. 1 and 2 for persons with 45 ml Thorotrast deposited in the RES. The smallest doses are in the terminal bronchi, and the largest in the trachea.

3. Doses from primary Thorotrast deposits

Hursh et al. (1957) analyzed the Th-232 content of tissues taken at autopsy from 4 cases, two of whom died a few weeks post injection and two at many years post injection. The volume of Thorotrast injected ranged from 40 ml to 75 ml, with an average value of 60 ml. On average the lungs contained 1.7 % as much Th-232 as the liver and spleen, and had dose rates of about 0.01 rads per day. Kaul (1964) found in measurements on one case only about 0.05 % of the total body Th-232 in the lungs, which gives dose rates negligible compared to the contribution from Tn in the breath. We do not know the origin of the difference between these observations, but it might reflect differences in the amount of lymphatic tissue contained in the organ samples.

Fig. 1



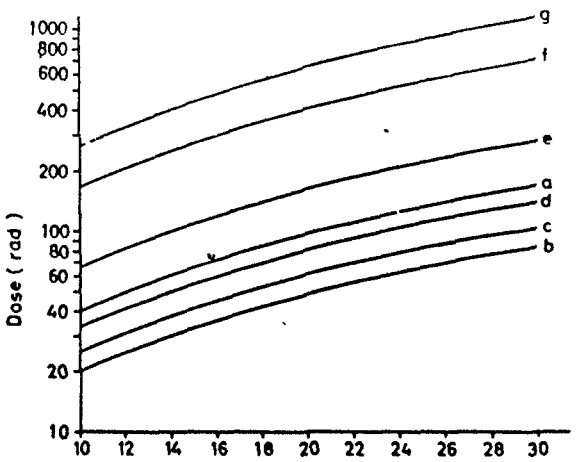
Time after Injection (years)

Doserate after injection of 1 µCi Th-232
(about 45 ml Thorotrast)

Thorotrast Deposits in RES

a) Resp. Zone
b) Terminal Br.
c) Subsegmental Br.
d) Segmental Br.
e) Lobar Br.
f) Main Br.
g) Trachea

Fig. 2



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a) Resp. Zone
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THE DOSES FROM THOROTRAST AND MIGRATED DESCENDANTS: STATUS, PROSPECTS, AND IMPLICATIONS

L.D. Marinelli

1. Introduction

The requirements of adequate dosimetry in Thorotrast-injected patients and most of the difficulties encountered have already been stated or implied by the preceding speakers. However, since our knowledge is still incomplete, the requirements of macro- and microdosimetry will be summarized first in general terms, and complemented later by suggestions for improvements needed to elucidate dosimetric questions which are still uncertain.

2. Macrodosimetry

The requirements of macrodosimetry are: (1) collection of representative samples, (2) localization of activity in vivo, (3) collateral studies with short-lived daughter products, (4) correlation of results between (1) and (2).

The attainment of these objectives is beset by many experimental difficulties. For instance, the measurement of the short-lived, but highly significant, daughters from Ra-224 to Tl-208 is hampered by the low level of activity involved and by the small number of useful representative samples available, since these can be obtained only if a high degree of time coordination is attained between physician, pathologist and physicist. Some of these difficulties may be eased by techniques involved in (2) above. Thus Kaul has already mentioned the successful combination of whole body counting with surgical procedures. Localization in vivo by means of collimated scanning deserves to be exploited to the fullest: May of our laboratory has measured the radioactivity of the legs of four Thorotrast patients and found it consistent with the estimates obtained from analysis of cortical bone (see Table 4). Of great interest also is the possibility of relating the exhalation rate of Rn-220 (Tn) with the activity of Pb-212 and daughters in the respiratory tract, since Schales mentions the detection of this activity over the chest of patients treated with Ra-224. Pertinent information can also be supplied by collateral studies in man or laboratory animals following judicious administration of members of the thorium chain. I refer to the studies on dogs described by Stover at this meeting and by Stover et al. (1960), to the work of Eridani et al. (1964) on bismuth in the rat, and to the investigations of Maletskos et al. (1964) and Schales (1964) on the kinetics and metabolism of Ra-224 and daughters in man. Experiments of this type should be designed to evaluate the biological half-life of a given daughter in the relevant biological compartment; hence, the usefulness of experiments with longer lived isotopes of Ra, Pb, Bi and Po should also be considered.

Another type of collateral study consists in comparing the equilibrium ratios of Th-228 descendants in the tissues of various species at relatively short times following the injection of Thorotrast. The results in

Table 1

Equilibrium of Th-228 descendants after Thorotrast I.V. injection
(Ra-224/Th-228, Pb-212/Th-228, Pb-212/Ra-224)

Animal	Duration of Burden	Liver			Spleen			Kidney			Reference
		Ra/Th	Pb/Th	Pb/Ra	Ra/Th	Pb/Th	Pb/Ra	Ra/Th	Pb/Th	Pb/Ra	
Beagle	21 d	0.55	0.19	0.34	0.37	0.19	0.51				Parr (1964)
Rat	35-38 d	0.55	0.40	0.73	0.43	0.23	0.53				"
"	1.0 yr	0.49			0.32						Simmons (Pers. Com.)
"	1.5 yr	0.52	0.25	0.48	0.39						"
"	2.0 yr	0.50	0.16	0.32	0.44						"
Man	50 d	0.59	0.32	0.54	0.69	0.26	0.38				Parr (1964)
"	14 yr	0.66	0.32	0.48	0.75	0.23	0.30				Rundo (1961)
"	Long	0.90	0.40	0.44	0.90	0.40	0.44				Kaul (1964)
"	Long							0.80	0.39	0.49	Oberhausen et al. (1964)

Table 1 show values after attainment of the short-term equilibrium of Ra-224 and Pb-212 vs. Th-228 in the liver and spleen of dog, rat and man. The data on rat extend from 35 days to 2 years, those in man from a few weeks to many years. One cannot but remain impressed by the following facts: (1) The Ra-224/Th-228 ratios at short times after injection are remarkably similar in liver, regardless of species; there is a definite increase in man at later times, fully consistent with data presented at this meeting and with the observations of Hursh et al. (1957) and Hursh (1965) on Ra-224 excretion and retention over 1000 days. (2) The liver Ra-224/Th-228 equilibrium ratios at short times are very similar to the Ra-228/Th-232 equilibrium ratios in humans at long times (see typical values for the latter in Table 2). (3) At shorter times in rats and dogs the Ra-224/Th-228 ratio in spleen is lower than in liver, but in man it seems to be higher.

These latter results are consistent with the idea that radium atoms, in escaping by recoil from the recently deposited colloidal particle, may spend more time in the spleen than in the liver of man and relatively less in the other two species. This effect is not, and should not be, evident with Ra-228; because of its much longer radioactive half-life this nuclide has more time to escape into the circulation.

One cannot be as explicit about the Pb-212/Ra-224 ratio. The results seem very consistent in man; however, the values on animals require confirmation beyond 38 days, since Parr's technique was not fully implemented in obtaining most of the data. The apparent time invariance of this ratio and its species dependence may be due to the escape of the noble gas Tn from the organs in question.

The values of Oberhausen et al. (1964) obtained from the kidney of man many years after retrograde pyelography fit in extremely well with the results in the reticuloendothelial system (RES): the Ra-224/Th-228 ratio is high in aged deposits and the Pb-212/Ra-224 ratio is similar to the values in liver and spleen, irrespective of time. These findings raise the question as to whether the equilibrium status of the chain, at least as far down as Th-228, is a property of the colloidal particle and not of the tissue in which it resides. As to the Ra-224/Th-228 ratio, it is evident that its increase with time after deposition is consistent with the various mechanisms discussed by Faber and Müller at this meeting.

3. Microdosimetry

In his conclusions Kaul mentioned the need to expore the localization of Thorotrast aggregates in the RES. I am sure that we all agree with him. A few suggestions as to methods which might be useful in this quest are: electron microscopy and microradiography (to study the aggregates), autoradiography (to determine types of cells at risk), tissue cultures and in vitro studies (to investigate intra- and extra-cellular migration of daughters).

One point is worth emphasis. The difficulties of correlating dosimetric parameters with the toxic effects of Thorotrast are, of course, increased when one considers the colloidal deposition in the RES, but this situation is not present in tissues where deposition results from trans-

Table 2

Whole-body balance of Thorotrast descendant activities
(Nanocuries per organ many years after 50 ml injection)

Tissue	Weight (g)	Th-232	Ra-228	Th-228	Ra-224	Rn-220 +Po-216	Pb-212	Bi-212	Po-212 +Tl-208
Whole body	70 000	1 250	625	625	556		500	500	500
Liver	1 600	950	425	420	378		190	130	
Spleen	175	120	60	58	52		26.5	18	
Red marrow	1 600	160	80	32	29		26	40	
Lung	800	6	3	2.4	2		24	24	
Lymph node and lymph	1 500	5	20	17	17.5		22.5	22	
Blood	5 300	-	4	4	11		72	150	
Kidney	310	1.5	0.3	0.6	2		2	3	
Skeleton	7 100	6.5	16.5	21.5	43		40	40	
Soft tissue	51 600	-	16.2	70.5	20		100	76	

80 % of Ra-224

Same as Bi-212

location of daughter products. The spotty distribution of radiation sources, per se, should not lead to undue concern, since the same problem is being faced by investigators interested in the toxicity of bone seekers.

4. Distribution of Thorotrast radionuclides in body

In Table 2 is shown an estimated typical distribution of radionuclides among the organs of the body many years after injection of 50 ml Thorotrast. In the RES the values are practically the same as Kaul's. One question does arise for the spleen, shown as containing 10 % of the Th-232 in contrast with the estimates of 21 % and 17 % by Rundo (1961) and Kaul (1964). The justification for the value in the table is the measurements of Parr in 4 human cases at 50 days post-injection and one case at 11 years. However, since the correct figure depends on accuracy of representative sampling, duration of burden, shrinkage, etc., it is obvious that more study is needed. Another question arises on the amount of Th-232 in the marrow; measurements reported by Hursh et al. (1957) and Parr (1964), when extrapolated to 1500 g, come to about 10 % - 15 % of the Th-232 burden. The value of 30 % which Kaul has obtained from his experiments and ours seems to rely on the extrapolation from the weight of bone sample to the entire bone marrow. This procedure is extremely difficult to justify because contamination, fractional marrow weight, etc., interfere with precise evaluation. There is no question in my mind that special attention will have to be devoted to this type of assay.

A task of some importance is also the measurement of the biological half life of Tn in the RES and elsewhere; this noble gas, undetained by chemical processes, should escape faster than any other member of the chain and should yield information on the diffusion rate. Moreover, this type of measurement may clarify why the ratio Tl-208/Ac-228 for the whole body in vivo varies from 0.66 to 0.94 (Dudley, 1965) although the exhalation rates obtained by various authors agree rather well among themselves.

In Table 2 the fraction of Tn and Po-216 produced by Ra-224 in the RES which disintegrates therein, has been assumed to be 80 % as suggested by Kaul (1964), Hursh (1965), Grillmaier et al. (1964), and Stahlhofen (1964a). This figure is based on the exhalation rates experimentally determined in various laboratories and on a reasonable average transit time in blood and lung.

The concentration of Pb-212 in the lungs is important for at least three reasons: (1) Tn concentration in air exhaled by Thorotrast patients is higher than working level concentrations of Rn-222 in uranium mines, (2) the lung dose contributed directly by exhaled Tn cannot be measured in situ, and (3) the disintegration of Pb-212 and daughters in the pulmonary circulation contributes to lung dose. Since exhaled Tn moves in the lung in a direction opposite to that of inhaled Rn accompanied by dust, calculations for the latter (Hanford Symposium, 1964; Lafuma and Medjedović, 1964) are of limited help. In my opinion, if it were not for the uncertainty in the transport times involved, the data of Lafuma (1964) on parabiotic pairs of mice (one of which exhaled the Rn inhaled by the other) would be directly applicable. The best that we can do at this time is to utilize the concentration of Pb-212 found in the lung by Parr (1964). To a first approximation, the concentration that he measured is consistent

with (1) an exhalation of Tn equal to about 10 % of that formed in the body (Hursh et al., 1957), (2) an average lifetime of the Tn atom in the lung of 0.4 min, (3) the amount of Pb-212 in a volume of 300 ml of trapped blood in that organ, and (4) the amount of Tn left in the lung at exitus.

As to the kidney, some attempt should be made to study the organ contents in vivo, since the concentrations of Pb-212 and Bi-212 which are expected following intravenous injections of these elements in dogs and rats (Mays et al., 1958 and Parr, 1964) have not been reported in man.

We conclude our comments on Table 2 by recalling that it represents a compromise of data on exhalation, blood concentrations, tissue samplings at various times, excretion of Ra-224 and Ra-228, and whole body counting of the ratio Tl-208/Ac-228 in vivo.

5. Dose rate to various tissues from each member of the thorium chain

The most doubtful part of my presentation is Table 3, where I have tried to describe the dose rates contributed in various tissues by each member of the Th-232 family at many years after the injection of 50 ml Thorotrast. A modicum of modesty is implicit in the blank spaces accorded to the beta-ray emitters, inasmuch as the accuracy of the data does not warrant acknowledgement of their existence.

The pertinent elements, their radioactive half lives, and the dosimetric constant, K, are shown in the first, second, and third columns, respectively. The dose rates for liver and spleen are, of course, the highest; if they are multiplied by 0.3 to account for self-absorption in the deposits, these values are practically identical with those given by Kaul. As shown, the doses to the skeleton, kidney and circulating blood are close to the maximum permissible limits set for the working population; hence, they are of more than passing interest. Attention must be paid to the fact that a quality factor equal to ten or more for α-radiation raises these values well above acceptable limits. Therefore, pathological examination of these tissues is highly desirable from the standpoint of radiation protection.

The marrow dose looms important, since leukemias and pancytopenias have been reported; some autoradiographs are necessary to identify more precisely the colloidal deposition. Owing to the extremely weak radioactivity, long exposures are necessary unless "enriched" Thorotrast is used. No hope of registering translocated Ra-224 plus daughters in marrow may be entertained because of their very short half lives.*

As shown in the table, the dose rates in the skeleton are twice the values given by Kaul at this meeting. This discrepancy should not be surprising at all for two reasons: (1) the bone samples available are usually contaminated with marrow, and (2) the equilibrium of the Th-232 chain in bone mineral runs exactly opposite to that existing in the RES. The main question is whether, in bone, Ra-224 is in equilibrium with Th-228, or whether it exists with higher activity because of migration from the RES.

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* Excellent autoradiographs of aspirated marrow smears were presented by Harriss at this meeting; it is not clear, however, what fraction of the dose generated by marrow α-rays is expended in bone.

Table 3

Maximum dose rates per 50 ml Thorotrast injection (rad/yr)

Element	Half life	K*	Liver	Spleen	Marrow	Bone	Kidney	Lung	Blood	Soft tissue
Th-232	1.4×10^{10} yr	74.5	44.0	66.0	7.4	0.07	0.35	0.5	-	-
Ra-228	5.8 yr	-	-	-	-	-	-	-	-	-
Th-228	1.90 yr	100	26.3	34.0	-	0.30	0.2	0.7	0.08	0.14
Ra-224	3.64 d	105	30.2	34.5	2.1	0.63	0.68	0.2	0.22	0.04
Rn-220 + Po-216	51 sec, 0.16 sec	-	36.0	43.0	5.5	1.31	1.5	6.9	1.96	0.07
Pb-212	10.6 hr	-	-	-	-	-	-	-	-	-
Bi-212	1 hr	-	2.8	4.0	0.9	0.21	0.4	1.0	0.50	0.05
Po-212	0.3 µsec	-	8.2	11.4	2.7	0.61	1.1	3.3	1.42	0.15
Tl-208	3 min	-	-	-	-	-	-	-	-	-
	TOTAL		147	192	23.6	3.1	4.2	12.6	4.2	0.45

* Dosimetric constant: rad/yr per nCi/g

The values selected in Table 3 are based on an excess of Ra-224. It has been assumed that, since Ra-224 is excreted, this element must have reached the blood from either the skeleton or the RES. In either case, it can be shown that it must be present in bone in amounts above those found for Th-228. I have used the computations of Reynolds (1957) which agree with the observed excretion rate of Ra-224, and, by implication, I assume that they should predict correctly the Ra-224 deposition in bone.

I am sure that the Ra-224 analysis of Kaul in the femur (30 days post mortem) contradicts what I have just said. By contrast I wish to state that in four patients whose tissues were analyzed by Parr 50 days after injection, and soon after death, the predictions of Reynolds' analysis were checked by activity measurements within experimental error in two cases; and in two others the discrepancies were no larger than 50 %. Under those conditions, however, the Ra-224/Th-228 ratio in the RES is lower than at later times, and therefore the value of this ratio in bone was higher than Kaul's.

As to the dose due to Tn plus Po-216, data obtained by Mays et al. (1958), Stover et al. (1960), and Maletskos (1964) do confirm the assumption that Tn is retained almost entirely in bone. What we need most at the present time is some realistic value of the partition of Ra-224 by the soft vs. mineral tissues, since it was not considered in Reynolds' calculation. We are encouraged, however, by the fact that these investigations are taking place at MIT.

6. Epidemiological importance of doses from Thorotrast and migrated daughters

In comparing the clinical and pathological findings in Thorotrast patients with other epidemiological series, we shall neglect liver and spleen since no other epidemiological study involving radiation effects is similar to this group of patients in regard to either the dosimetric parameters or the possibility of chemical toxicity. The dose to the skeleton of Thorotrast cases, however, is of particular importance, despite its low magnitude. Table 4 shows the dose rates accruing to the populations most likely to supply epidemiological information on the effects of radiation on the skeleton. The total dose rates are shown at the right under the assumption of a quality factor of 1, 10, and 100 for α-radiation. The highest values pertain to the eventualities foreseen by the RBE Committee (1963).

Some comments are in order on Table 4. The USA population now under study because of the high Ra-226 content of its drinking water is at present composed of 600,000 people. Results of a retrospective study will be available soon. The highest dose rates in Table 4 are found in the Ra-226 dial painters for whom no untoward effects have been shown at the maximum permissible burden, 0.1 μCi. The lack of bone pathology in known Thorotrast cases, numbering as of today more than 2000 and bearing burdens equivalent to 1/6 to 1/2 of this amount, adds a much needed support to the choice of the maximum permissible burden of Ra-226, which is based on studies of the smaller population of radium dial painters. We hope that comparable information will be forthcoming from studies of miners and, above all, from residents of monazite regions who are much more numerous.

Table 4

Dose rate to bone

Exposure	Millirads per year						Rems per year		
	External γ + μ	K-40	From α-Radiation				Quality factor		
			Ra-226+d	Ra-228+d	Pb-210+d	Total α	1	10	100
Natural Bckgd.[a]	100	15	0.9	0.7	4.1	5.7	0.12	0.17	0.68
"High" Ra-226 water	100	15	7.0	7.7	4.4	19.1	0.135	0.31	2.03
Thorotrast injection									
Tissue sample	100	15	0.9	3100	4.1	3100	3.2	31.0	310
In vivo	100	15	-	6000	-	6000	6.0	60.0	600
Uranium mines	5000[b]	15	15.0	(5)	200	220	5.2	7.2	27.0
Ra-226 injection (0.5 μCi burden)	100	15	14500	-	6800	21000	21.1	210	2100
Residence over monazite	2600[c]	15	6.0[d]	(2.3)	4.6	13.0	2.6	2.7	3.9

(a) Midwest U.S.A.

(b) According to maximum permissible limits

(c) First approximation: data from Guarapari, Brazil (Penna Franca et al., 1965)

(d) From estimates at Kerala (Chhabra, 1964)

It is of some interest to examine the implications of the estimate made by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) on the incidence of osteosarcoma in the radium poisoning cases. This incidence has been stated to be about 4 cases/10^6/year/rad, as compared to 1 or 2 for the incidence of leukemia in the irradiated populations of Hiroshima and Nagasaki and in the x-ray treated patients suffering from ankylosing spondylitis. The Thorotrast population offers an opportunity to estimate within itself the ratio of the incidence of osteogenic sarcoma to that of leukemia and to compare it to the ratio of the dose rates accruing to skeleton and marrow. If linear extrapolation applies, the incidence of osteogenic sarcoma should be from 2 to 4 times the leukemia incidence rate multiplied by the ratio of the skeletal dose rate to that of the marrow. Since this dose ratio has been estimated as low as 1/20 (1.5/25) (Kaul) and as high as 6.0/23 = 1/4 (Table 4), the osteosarcoma rate should range from as low as (2 x 0.05) = 0.1 to as high as (4 x 6.0)/23 = 1.0 times the leukemia incidence within the Thorotrast population. This ratio, conceivably, could be extended to 0.3 - 3.0 if one assumes that the oncogenic effectiveness per rad in bone (but not in marrow) is three times as high for Th-228 as for Ra-226, as some of the results at the University of Utah seem to imply from the incidence of tumors in the beagle skeleton. It is obvious that if the higher figures were correct, our medical colleagues would have confirmed it already. Lack of bone lesions at this stage may imply that the latent period for osteogenic sarcoma is much longer than for leukemia, or that the quality for α-radiation is remarkably different for the two effects. The possibility remains that α-radiation in bone from Thorotrast may be less carcinogenic than in the radium poisoning cases because it is more evenly distributed. This issue, to my knowledge, is still undecided.

I shall not dwell any longer on this point, but simply remark that this elementary calculation illustrates very vividly the importance of follow-up in the Thorotrast population. It is obvious also that to enhance the usefulness that laborious epidemiological investigations deserve, the dose rates in bone and marrow must be determined to a higher degree of accuracy.

7. Epidemiological studies involving the lung

We turn our attention to the dose absorbed by the lung under the various types of exposure indicated in the first column of Table 5. In the first two categories the doses to the various portions of the respiratory tract are shown; they were obtained directly or extrapolated from the data of Jacobi (1964). It is obvious that mining operations lead to the highest doses in the lower bronchial tree. Next in importance is the Thorotrast series wherein the average dose to the whole lung is estimated to be 1/2 the dose to a portion of the bronchial epithelium of the miner.

Lack of lung pathology in the Thorotrast group is encouraging, in the sense that it suggests that it may be possible to obtain effective control of lung pathology in miners by paying as much attention to the curtailment of inhaled dust as has been paid to the dilution of radon by forced ventilation. However, one must realize that not much can be said at this time.

Table 5

Dose rate to lungs

Exposure	Tissue	Millirads per year: External Radiation	α-Radiation: Rn-222+d	α-Radiation: Th-228+d	α-Radiation: Internal α[b]	α-Radiation: Total α	Rems per year, Quality factor: 1	10	100
Natural Bckgd[a] 0.1 pCi/l Rn + 0.2 pCi/l Tn	Alveoli	115	4.4	0.9	0.1	5.4	0.120	0.170	0.66
	Bronchi	115	5.6	0.1	0.1	5.8	0.121	0.17	0.70
	" (SQ)	115	140	4.2	0.1	145	0.260	1.56	14.6
	Trachea	115	27	1.0	0.1	28	0.143	0.4	3.0
Mining operations[a] 100 pCi/l Rn + 100 pCi/l daughters	Alveoli	5000	720	-	20	740	5.7	12.4	790
	Bronchi	"	720	-	20	740	5.7	12.4	790
	" (SQ)	"	21000	-	20	21000	26.0	215	2100
	Trachea	"	38000	-	20	3800	88	43	385
50 ml Thorotrast 3.6 x 10^4 pCi/m	Entire lung (Av)	115	-	12600[c]		12600	12.7	126	1260
0.5 μCi Ra-226 5 pCi/l, Rn exhaled	Entire lung (Av)	115	8.5[d]	-	-	9	0.12	0.2	1.0
Cigarette smoker[e]	Bronchial Epithelium	115	6.6	-	-	6.6	6.6 min. 40 max.		

(a) Jacobi (1964)

(b) 1/4 average dose to osteocytes (20 vs 80 % retention at continual intake)

(c) Po-216 + Pb-212 + Bi-212 from Pb-212 tissue analysis (consistent with exhalation rates)

(d) From data on pure Rn inhalation: blood/lung ratios in mice (Pohl, 1964)

(e) Radford and Hunt (1964)

Much has been written on Po-210 contained in tobacco and on its deposition in some regions of the bronchial tree; in our laboratory Holtzman has confirmed the existence of higher Po-210 concentration in the lungs of smokers as compared to non-smokers. The dosimetric implication of these findings is in a preliminary state.

It is pertinent to ask at this point whether the lungs of the patients irradiated for ankylosing spondylitis have not been subjected to considerable irradiation and whether an epidemiological survey on lung damage in this population does not deserve as much attention as the leukemia survey.

Anticipating some findings of lung pathology, it may not be entirely amiss to extend the estimates of UNSCEAR to the lung of the Thorotrast patient in order to establish whether a more exact statistical study is warranted as epidemiological observations accumulate. We observe that for a typical 25-ml Thorotrast injection, the lungs will sustain a dose rate of 6.3 rads of α-radiation per year. If a quality factor of 2.5 is assumed, this rate is equivalent to about 15 rem per year. Three other assumptions will be made: (1) that the average time at risk for each patient is 15 years, (2) that the incidence of radiation-induced carcinoma of the lung is equal to that of leukemia, namely $1.5/10^6$/year/rad, and (3) that the latent period is about 5 years. The incidence, calculated by multiplying these numbers, comes out to be 1.6 cases per thousand, a figure not entirely beyond detection if careful follow-ups of non-smokers (women?) among Thorotrast cases are pursued. If the RBE of the thorium family is higher than that considered here, the higher incidence would be much more easily detected.

8. Epidemiological studies involving bone marrow

Last but not least, we must consider the dose to the marrow which has come under close scrutiny by UNSCEAR, inasmuch as both the Atomic Bomb Casualty Commission study and the spondylitis experience seem to indicate a radiation-produced incidence of leukemia of $1/10^6$/year/rad. If one considers that in Table 6 the doses to the marrow of Thorotrast patients are on the conservative side, one cannot but be impressed by the importance of the Thorotrast group, especially when the data of Silva Horta et al. (1965), and of Faber and Telles presented at this meeting, imply that derangements of marrow have been observed. If one applies the formulas of UNSCEAR to a 25 ml injection of Thorotrast with the same proviso adopted in the case of the lung, one finds an incidence of 3 cases per thousand on the assumption of the dose rates considered here, and about 4 cases per thousand if the doses proposed by Kaul are more representative.

9. Conclusion

In conclusion, with regard to our present knowledge already at hand, it is clear that every effort must be made to obtain good dosimetric and epidemiological information pertaining to the marrow, the lung, and bone. Studies to include the kidney and lymphatic system of these patients should be considered since, under equilibrium conditions, the absorbed doses to these tissues may be appreciable. At a later time, as more information is acquired, a comparison of dosimetric and pathological findings in the

Table 6

Dose rate to marrow

Exposure	Millirads per year						Rems per year		
	External		α-Radiation				Quality factor		
	γ + μ	K-40	Ra-226+d	Ra-228+d	Pb-210+d	Total α	1	10	100
Natural Bckgd.[a]	100	15	0.1	0.07	0.4	0.6	0.11	0.12	0.17
"High" Ra-226 water	100	15	0.7	0.77	0.44	1.9	0.12	0.13	0.31
Residence over monazite	2600[b]	15	0.6[c]	(0.23)	0.46	1.3	2.6	2.6	2.7
Uranium mines	5000	15	1.5	0.5	20	22	5.0	5.2	7.2
Ra-226 burden (0.5 μCi)	100	15	145	-	680	2100	2.2	21	210
Thorotrast injection (50 ml)	100	15	0.1	24000	0.4	24000	24.1	240	2400

(a) Midwest U.S.A. (via bone concentration and Kononenko formulae (Kononenko, 1957)

(b) Preliminary data from Guarapari, Brazil (Penna Franca et al., 1965)

(c) From estimates of bone burden at Kerala (Chhabra, 1964)

kidneys of miners may be justified because the concentration of Po-210 therein may be considerable.

Finally, I would like to encourage the statisticians connected with these studies to begin some preliminary evaluation of the incidence of pathology versus the man-rad-years at risk in order to enrich the very modest patrimony of facts pertaining to the delayed effects of low-level chronic irradiation.

CLINICAL AND LABORATORY ALTERATIONS IN THOROTRAST RECIPIENTS

N.C. Telles

1. Introduction

In recent years there have been an increasing number of reports attesting to the seriousness of the delayed effects of injected Thorotrast (Blomberget al., 1963; Silva Horta et al., 1965; Silva Horta, 1956; Looney, 1960). Depending upon the route of injection these effects have centered largely in the reticolo-endothelial system of the liver, spleen and bone marrow, or they have concerned other organs or anatomical structures into which Thorotrast may have been injected.

The radiographic diagnostic applications of Thorotrast were varied but its potential dangers were warned of very early in its use (Council on Pharmacy and Chemistry, 1932; Reeves and Stuck, 1938; Whitacker et al.; 1933). Experimental studies established its carcinogenicity in animals (Oberling and Guerin, 1933; Selbie, 1938), but early studies in man failed to show any notable effect within a few years after its use (Yater and Whitmore, 1938; Yater and Coe, 1943).

In 1947 there appeared the first report of a primary liver tumor related to Thorotrast (MacMahon et al., 1947). There has since followed a succession of reports describing the untoward effects of Thorotrast in the liver and other sites. Several excellent papers reviewing these problems and related aspects have appeared (Silva Horta, 1956; Looney, 1960; Silva Horta, 1951; Dahlgren, 1961; Buda et al., 1963; Thomas et al., 1951).

The purpose of the present report is to review some of the clinical and laboratory alterations which have been observed as delayed effects in Thorotrast recipients. No attempt has been made to cover pathological changes or experimental studies. Although both local as well as intravascular injections will be considered,most attention will be given to effects following intravascular injections of Thorotrast.

2. Physical findings in Thorotrast recipients

The onset of physical findings depends on how long the patient has carried the Thorotrast, the amount of Thorotrast injected, the nature of the problem for which the injection was originally given, the medical history prior to and after receiving the Thorotrast, and other factors. In certain instances of cerebral arteriography where negative diagnostic results were obtained at the time of Thorotrast injection, the diagnosis of no-disease-found was frequently made and the patients have remained symptom-free to the present day. At the other extreme the clinical history might be that of a case (Ellis, 1964) in which a suprasellar meningioma was removed following which the patient remained in good health for 26 years, except for the loss of sight in one eye. The patient then presented with symptoms of ankle and leg edema. Ascites developed, liver failure quickly ensued and the patient died, apparently within a few months after the onset of his symptoms with a bile duct tumor.

The vital signs in these patients of course reflect the clinical status of the patient at the time he is seen and this may or may not be related to delayed effects of Thorotrast. Thus, individuals with Thorotrast have died with cerebrovascular accidents or myocardial failure, with little or no evidence of Thorotrast effects. As such the usefulness of vital signs can best be judged only in terms of the problems that bring the patient to the hospital.

The stigmata of chronic liver disease are frequently seen in Thorotrast cases. Mild to intense jaundice, vascular angiomata, palmar erythema, easy bruisability, muscular wasting, dark urine, melena, ascites, edema, lethargy, easy fatigability and weight loss have all either been noted or complained of by patients. Enlargement of liver or spleen is frequently noted on examination. Testicular atrophy is not uncommonly reported, as is gynecomastia.

On occasion certain of these findings have been reported in unusual and interesting circumstances. In a recent report of Hodgkin's disease associated with Thorotrast (Verner and Smith, 1963), the patient was noted to have weight loss, polyuria, polydipsia and polyphagia. Physical examination revealed marked wasting, signs of cardiac failure, sceral icterus, abdominal ascites and dependent edema. The patient had a progressively downhill course and died in an apparent hepato-renal syndrome. At autopsy the liver showed only minimal periportal fibrosis. The unusual finding was that of abdominal Hodgkin's disease, the first reported case in association with Thorotrast injection.

Another similarly interesting case is that of a Kaposi-like sarcoma developing in an individual who received Thorotrast for investigation of abdominal pain at age 17 years (Perkins et al., 1960). No diagnosis was made at that time and his symptoms subsided. Thirteen years later he developed an enlarged supraclavicular lymph node which was excised but failed to show any neoplasm. Nonetheless the area was treated with local irradiation. Eighteen years after the Thorotrast injection anemia was found. Epigastric pain developed and an enlarged liver was noted. The patient rapidly developed liver failure and died. Autopsy showed tumor involving the liver, spleen, bone marrow, lymph nodes, kidneys and adrenal glands. No lesions of the skin were noted, no relationship to the local irradiation was implied.

Thorotrast, in addition to its use in cerebral arteriography, aortography and hepato-splenography, was widely used for pyelography, mammography, cerebral ventriculography, myelography and injection of sinus tracts and cavities. Complications following the use of Thorotrast in these procedures have been reported. In general, progressive pain and functional disability of the organ or part involved have characterized these complications. Silva Horta (1956) has cited these problems, as have others (Gough, 1963; Brady et al., 1960; Levowitz et al., 1963; Nijnders et al., 1963; Budin and Gershon-Cohen, 1956; Mora, 1940; Barry and Rominger, 1964).

Perivascular injection of Thorotrast usually leads to progressive induration at the site of injection. Pain, distal paresthesiae and other sequelae due to local encroachment of nerves, blood vessels and other organs by the progressive fibrosis in the Thorotrast granuloma

have been observed. Recent cases of granulomas in the neck have reported hoarseness due to vocal cord paralysis, Horner's syndrome, tracheal pressure with signs of respiratory diseases at times (Gough, 1963; Levowitz et al., 1963; Barry and Dominger, 1964). Silva Horta (1956) reported that one case known to him required urgent tracheostomy.

Compression of the carotid and jugular vessels as well as involvement of vessels in the antecubital fossa and femoral triangle has occurred. Stiffness of the neck or limbs has been common with limitation of motion or debility of the part involved.

Renal changes following pyelography with Thorotrast have also been seen (Silva Horta, 1956; Rijnders et al., 1963). The clinical findings generally result from renal pelvis granulomas or carcinoma, and involvement of the ureters. These include radiating lumbar pain, which may have sudden onset. Also fever, chills, headaches, dysuria, pyuria, and hematuria have been part of the clinical picture.

Thorotrast tumors or granulomas of the breast have been reported. No discharge from the nipples has been described, but pain and tenderness in a freely movable, fluctuant mass was described by Budin and Gershon-Cohen (1956) in their case report of a breast carcinoma developing seventeen years after mammography with Thorotrast.

Carcinoma of the maxillary sinuses has been another complication (Kligerman et al., 1960; Buda et al., 1963; Feldman et al., 1963). Asymptomatic swelling of the palate was the presenting symptom in one patient. Double vision, proptosis and anesthesia of the upper lip and nasal side of the face were the complaints in another case. Nasal discharges, oro-antral fistulae, and loosening of teeth have been among the other complaints which have led these patients to see their physician.

Another recent case is the first report of a meningioma induced by Thorotrast (Kyle et al., 1963). Progressive loss of hearing, blurred vision and finally onset of seizures preceded the hospitalization of the patient. Weakness in the extremities, abnormal deep tendon reflexes as well as absent abdominal reflexes were found. Following surgery the patient's motor deficit cleared and vision improved.

Of equal interest is one report of a woman with an undifferentiated peritoneal carcinoma who had undergone a sterility investigation in which Thorotrast was used (Cattell and Kahn, 1960). Large amounts of the Thorotrast spilled into the peritoneum, this apparently being the etiologic agent for her carcinoma. On admission to the hospital the physical findings were limited to the abdomen with tenderness and an enlarged uterine fundus being the only notable features.

Progressive myelopathy was reported in three cases following myelography with Thorotrast (Maltby, 1964). Stiffening in the legs, paresthesiae, stress incontinence and difficulty in initiating urination were early symptoms in one case. Later, depressed deep tendon reflexes and weakness of the lower extremities were observed. Severe pains in the legs required a cordotomy, following which bladder and bowel dysfunction led to a urinary tract infection, progressive renal failure and death. The interval between Thorotrast myelography and death was 15 years. The

other two reported cases were of similar nature with cord bladder and progressive weakness, pain and debility of the lower extremities, accompanied by reflex and sensory changes.

The above resume of clinical observations very obviously does not include all physical findings which have been described in Thorotrast recipients. They are felt to be representative of the kind of positive findings these patients may present to the examining physician. It is of some interest to note the clinical findings in a relatively asymptomatic group of patients examined at the University of Michigan and Massachusetts Institute of Technology (Table 1a, b).*

These patients received Thorotrast largely for cerebral arteriographic studies. Only case T3 (i.e., MIT 3) appeared to have a clear-cut history of precedent liver disease. He had had a spleno-renal shunt with splenectomy for esophageal varicies. His liver was enlarged, but he was still ambulatory and able to undergo whole-body counting at MIT. Two other patients (M4, M7) had palpable liver edges, but they were asymptomatic and in good health with no history of liver disease. One of these patients (M7) had an elevated bromsulphalein retention.

The significance of the physical findings in these last two patients is difficult to assess, but they should not be overlooked even though in one patient all clinical parameters tested were negative, and only the bromsulphalein retention was abnormal in the other. Careful follow-up in these patients will be extremely important.

It would seem that while the physical evaluation of Thorotrast patients cannot be regarded as a sensitive measure of Thorotrast effects except in the later stages of these effects, careful evaluation may at times pick up an unexpected finding such as enlargement of the liver in the otherwise asymptomatic patient. The frequency and significance of such occurrences still remain to be established.

3. Liver function studies

Table 2 presents some results of liver function studies done on Thorotrast recipients studied at the University of Michigan and MIT. The average retention period of Thorotrast for both of these groups was about 16 years. No history of liver disease was recorded in the Michigan group (but one patient had a history of alcohol intake). In the MIT group, one patient had a history of previous liver disease probably due to alcoholic cirrhosis (T3).

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* In this report the author is privileged to present clinical data made available to him by Dr. Fred J. Hodges, University of Michigan, which were gathered as part of a Thorotrast study supported by the USPHS, Division of Radiological Health; and also data which have been collected and reported by Dr. Robley D. Evans and the Radioactivity Center, Massachusetts Institute of Technology in the Annual Reports (MIT Annual Report - 1960 Report; 1961 TID-13328; 1962 TID-16349; 1963 NYO 9505; 1964 MIT-952-1), as part of their long-term studies of radium and mesothorium toxicity.

Table 1a

Clinical findings in Thorotrast recipients

Patient No.	Sex	Retention (yrs.)	TST Dose (ml)	Age at Exposure	Present Health	Past History (with reason for TST)	Recent Complaints and Physical Findings	X-Ray Findings
UM 1	F	17	NA	43	Poor	1939 - Total Hysterectomy 1947 - TST for lt. parietal hemangioma which was excised 1951 - Adenocarcinoma of thyroid excised 1964 - Carcinoma of colon (current)	Admitted to hospital with complaints of abdominal pain, melena, fatigue. Liver and spleen not enlarged. Slight pedal edema. Barium enema revealed carcinoma of colon, diverticulitis.	Chest-cardiomegaly. Abd.-TST in L, S, PN. Long bones negative. TST injection site negative.
UM 2	F	15	28	46	Good	1949 - Aneurysm of rt. int. carotid artery shown by TST 1963 - Biopsy "skin cancer", lt. arm 1963 - Neuro-surgery clinic, ? anxiety; seizures, on Dilantin	Complaints of strange sensations origniating in legs and passing up to head. Liver and spleen not enlarged. CNS-negative	Chest-negative. Abd.-TST in L, S, PN. Long bones negative TST injection site negative
UM 3	M	15	27	NA	Good	1949 - Severe occipital headaches with memory loss, rt. carotid arteriogram with TST was negative. Final diagnosis: Probable old subarachnoid hemorrhage.	No complaints. Liver and spleen not enlarged. CNS-negative.	Chest-negative Abd.-TST in L, S, PN. Long bones negative. TST injection site negative.
UM 4	M	16	36	19	Good	1948 - Grand-mal and rt. Jacksonian seizures. Lt. carotid arteriogram was normal. Diagnosis: Post-traumatic epilepsy from early head injury.	No complaints. On anti-convulsant therapy. Liver down 2 finger breadths, smooth. Spleen, not felt.	Chest-1.5 cm. nodule, rt. lower lobe. Abd.-TST in L, S, PN. Long bones negative. TST injection site negativ
UM 5	M	15	30	33	Good	1949 - Rt. sided Jacksonian seizures. Lt. carotid arteriogram was negative.	No complaints. Liver and spleen not felt. CNS-neg.	Chest-negative. Abd.-TST in L, S, PN. Long bones negative. TST injection site negative.
UM 6	M	15	30	28	Good	1928 - Onset grand-mal disorder 1949 - Lt. carotid arteriogram was negative.	No complaints. Liver and spleen not felt. Moderate dysarthria. Positive bilateral Babinski.	Chest-negative. Abd.-TST in L, S, PN. Long bones negative. Some TST at injection site in neck.
UM 7	M	12	60	50	Good	1952 - Fell and struck head. Bilateral carotid arteriograms were negative. Had previous history of alcoholic intake.	No complaints. Induration noted at TST injection site. Liver edge down 1 fb. CNS-negative.	Chest-negative. Abd.-TST in L, S, PN. Long bones negative. Large amount of TST in rt. neck.
UM 8	F	21	NA	42	Good	1943 - Lt. frontal meningioma removed following TST injection. Post-operative seizures. 1962 - Lt. frontal craniotomy, hematoma removed from previous operative site.	No complaints. Liver and spleen not felt. CNS-negative	Chest-negative. Abd.-TST in L, S, PN. Long bones negative. TST injection site negative.
UM 9	F	15	30	NA	Good	1949 - Bruit lt. forehead. Lt. carotid arteriovenous malformations. Ligation of lt. internal and external carotids done. 1956 - D & C for uterine bleeding.	No complaints. Liver and spleen not felt.	Chest - TST in mediastinum. Abd.-TST in L, S, PN. Long bones negative. TST injection site negative.
UM 10	M	23	16	12	Good	1941 - Grand-mal seizures. Rt. carotid arteriogram was negative.	No complaints. Still on anti-convulsant therapy. Liver and spleen not felt.	Chest-TST in mediastinum. Abd.-TST in L, S, PN. Long bones negative. TST injection site-negative.

Table 1b

Clinical findings in Thorotrast recipients

Patient No.	Sex	Retention (yrs.)	Ra-228 burden (μCi)	Age at Exposure	Present Health	Past Medical History (with reason for TST)	Recent Complaints and Physical Findings	X-Ray Findings
MIT 1	M	10	0.149	54	Good	1954 - Apparent stroke while driving automobile. Dysarthria. TST used. Results of study not available.	No complaints. Liver and spleen not felt. Neuro-muscular-atrophy lt. arm. CNS-lt. ankle clonus. Babinski positive on lt. Absolute paralysis lt. arm. Paresis, lt. leg.	Abd.-TST in L, S. Long bones-osteoporosis, due to left hemiparesis. Injection site negative.
MIT 2	M	11	0.17	23	Fair	1943 - Head injury, followed by progressive loss of vision, left eye. Headaches, syncope. 1947 - TST injection. No pathology noted.	No complaints. Liver and spleen not felt.	Chest-negative Abd.-TST in S, PN.
MIT 3	M	13	0.34	43	Poor	1950 - TST for hepato-splenography. Denies alcohol but has had multiple admissions for gastro-intestinal bleeding from esophageal varices. Spleno-renal shunt and splenectomy in 1950.	Complaints of weakness, easy fatigability. Lungs-basilar rales. Heart enlarged. Liver down 4 finger breadths.	Abd.-TST in L, PN. Spleen -absent. Long bones negative
MIT 4	M	17	0.48	49	Fair	1943 - Excision of ischio-rectal abcess. 1943 - Hepato-splenogram for liver abcess. 1945 - Barbiturate addiction. 1951 - Radioactive I-131 for toxic goiter 1953 - Coronary thrombosis	Complaints of intermittent angina. Liver and spleen not felt.	Chest-TST in mediastinum. Abd.-TST in L, S, PN. Long bones-TST extravasated in rt. upper leg.
MIT 5	M	26	0.145	40	Poor	1934 - Aneurysm of rt. carotid removed. Past history of gastric ulcer.	Asthma-5 yrs, duration, ? etiology. Decreased vision rt. eye. Induration rt. neck. Liver and spleen not felt. Limitation of motion in rt. shoulder.	Neck-TST deposit Abd.-NA Long bones negative.
MIT 6	F		0.025	NA	Poor	Multiple operations including hysterectomy, cholecystectomy and sympathectomy. Reason for TST not known. Was also radium dial painter.	Multi-system complaints. Horner's syndrome. Neck negative. Liver and spleen not felt.	No TST noted. Abdominal metal clips noted.
MIT 7	F	13	0.085	47	Fair	1948 - Carotid arteriograms for rt. sided headaches and Horner's syndrome. 1959 - Epigastric pain with tarry stools, GI series negative except for TST in L, S. 1964 - Recurrent epigastric pain. Liver biopsy and bone marrow negative. Attempt to remove TST with DTPA failed. Dx: Pancreatitis.	Recurrent abdominal pain. Epigastric tenderness on deep palpation. Liver and spleen not felt.	Abd.-TST in L, S.

Key to Symbols:

TST	- Thorotrast	M	- male
L	- liver	NA	- not available
S	- spleen	CNS	- central nervous system
PN	- portal lymph nodes	UM	- University of Michigan Subjects
F	- female	MIT	- MIT Subjects

Except for the latter patient and patient M1 (who was hospitalized at the time of study with diverticulitis and cancer of the large bowel), the tests recorded are almost all within normal limits. One exception is the bromsulphalein retention which was elevated above normal in 6 of the 10 patients on whom it was successfully performed.

It is of interest to compare this group of patients to those reported by Looney (1960). In his Group I, Looney reported 14 patients who had liver function tests. All had negative histories for liver disease. All had received doses of Thorotrast ranging between 15-25 ml. Only one had an abnormal bromsulphalein retention. The average retention period for Looney's group was 15.6 years.

For the groups reported in this paper the average retention period was similar to Looney's. For those who had a bromsulphalein test, the average dose of Thorotrast injected was about 32 ml. It might appear, therefore, that a dose-dependent effect could be at hand in these observations. However, the meagerness of the data, plus the uncertainties in them and in the comparability to Looney's data cautions that no conclusions be drawn. It may be worth noting that in Looney's high dose group (60 to 75 ml of Thorotrast) abnormal liver function tests were noted. Several of the patients in this group, however, had a history of previous liver disease.

The other unusual finding in the liver studies reported here is in the electrophoresis pattern of the serum proteins. Unfortunately, the normal range of values for the various serum globulins is not available for the Michigan patients at the moment. However, a comparison to normal ranges reported in the literature and given for the MIT group, indicates that for both the Michigan and MIT groups there appears to be a decrease in the amount of α-1 globulin present in a majority of the patients. This interesting observation will require further investigation.

Terminally, one or more liver function tests becomes frankly abnormal in most Thorotrast injection cases. This fact has been cited by Silva Horta (1956), who in addition notes several instances in which dysproteinemias were observed, including one in which the γ-globulin fraction of blood proteins was elevated. Sposito and Petroni (1961) made a similar observation.

The abnormal tests tend to reflect both the structural and functional liver damage produced by the Thorotrast. Frequently mentioned are abnormal blood proteins, alkaline phosphatase, serum bilirubin, abnormal prothrombin time, abnormal flocculation tests, serum cholesterol and cholesterol-esters, and a prolonged bromsulphalein retention.

One of the major difficulties in selecting tests of liver function is that most are non-specific. Combinations of tests have been advocated (Lichtman, 1954). In more recent years, other tests of liver function have been recorded, such as assays for serum glutamic-pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT). These enzymes are elevated in a number of liver diseases including viral hepatitis, Laennec's cirrhosis, biliary cirrhosis as well as metastatic and primary hepatic cancer. How useful these or other liver tests will be in assessing the clinically asymptomatic patient is still to be determined. In those Thorotrast cases where these enzymes have been recorded, they have often been elevated.

Table 2
Laboratory studies in Thorotrast recipients (this report)

Patient Number	Retention Period (yrs.)	TST* Dose (ml)	Blood Protein	Albumin	Globulin	Electrophoresis (given as % of total protein) α_1	α_2	β	γ	Ceph. Flocc.	Thy. Turb.	Alk. P'Tase	BSP	CA	P	BUN	Blood Sugar
UM 1	17	**	5.7	3.6	2.1	3.7	15.7	14.1	16.1	0	2.3	5.8		8.1	2.8		
UM 2	15	28	6.7	4.4	2.3	1.3	9.1	9.6	8.2	0	1.1	8.5	8	9.0	3.8		
UM 3	15	27	7.9	4.5	3.4	3.1	13.1	12.2	21.3	0	3.0	5.7	23	8.6	2.4		
UM 4	16	36	7.2	4.5	2.7	1.5	10.5	9.0	10.5	0		9.8	1	9.4	1.7		
UM 5	15	30	8.6	3.0						0	2.4	12.1	1	9.6	3.2		
UM 6	15	30	6.9	5.2	1.7	2.9	12.1	9.6	11.2	0	2.7	9.1	2	9.2	3.0	15	73
UM 7	12	60	6.5	4.3	2.2	1.7	8.5	13.0	19.3	0	2.3	8.1	11	8.6	2.7		
UM 8	21		6.5	4.9	1.6	1.8	8.4	10.2	14.4	0	1.3	6.5	21	9.1	3.4		
UM 9	15	30	8.0	4.5	3.5	1.7	10.4	12.5	22.2	0	2.2	8.8	4	9.3	3.0		
UM 10	23	16	6.6			1.3	9.8	12.1	14.3	0	1.8	7.5	13	9.4	3.3		
MIT 1	10		7.0	4.5	2.5	2.8	7.1	11.4	14.3			4.3				12	94
MIT 2	11		6.8	4.1	2.7	3.7	9.6	9.9	16.2	neg	1.0	3.0				23	126
MIT 3	10 13		6.1 8.1	3.2 3.9	2.9 4.2	3.0 3.5	7.9 6.4	12.1 13.6	24.3 28.4		1.0	12.4 8.1				13 20	152 139
MIT 4	17		6.7	4.1	2.6	3.7	7.3	9.4	19.1	neg	3.0	6.8				18	121
MIT 5	26		6.2	4.0	2.2	3.4	8.2	11.3	12.6		1.1	10.0				17	115
MIT 6			7.5	4.0	3.5	5.9	7.6	11.8	21.0			6.4				12	105
MIT 7	13									neg	4	33	12			NPN 39	100

Normal Lab. Values:

	Blood Prot.	Alb.	Glob.	α_1	α_2	β	γ	Ceph. Flocc.	Thy. Turb.	Alk. ** P'tase	BSP Retent.	Ca	P	BUN	Blood Sugar
UM	6.8-8.5	4.0-5.5	1.5-3.5	NA	NA	NA	NA	0-1	0-5	4-12	6	9-11	2.5-4.2		
MIT	6-8	3.5-4.5	2.5-3.5	3.7-8.3	6.2-11.6	10.0-16.6	10.0-20.0	neg	NA	1-4	5	9.5-11.5	2.5-3.5	8-20	80-120

** L of M (King-Armstrong Units)

MIT (Bodansky Units)

* TST = Thorotrast (intravenous or intra-arterial)

** Blank Spaces indicate data not available

There is, of course, considerable variability in reporting laboratory tests in the literature. Table 3 is a compilation of some tests which have been reported. It includes liver function tests and a few others. The table covers only a fraction of the cases available. With few exceptions these data were obtained during the terminal hospitalizations of the patients involved. Therefore, the problems that attend interpretations of the usefulness of laboratory data obtained under such circumstances should be kept in mind.

Table 3

Laboratory studies in Thorotrast recipients *

Test	Times reported	Results H	N	L	Test	Times reported	Results H	N	L
Total protein	17	0	11	6	B S P	10	10	0	-
Albumin	15	0	5	10	Bilirubin	16	8	8	-
Globulin	15	10	5	0	Prothrombin	7	-	4	3
Alk. P'tase	11	9	2	0	SGOT	6	3	3	-
Cholesterol	7	2	4	1	SGPT	3	1	2	-
Ceph. flocc.	5	5	0	-	LDH	1	1	0	-
Thymol turb.	14	12	2	-	Blood sugar	11	3	8	0
Sed. rate	14	5	9	-	Blood urea	14	4	10	0
Amylase	5	1	4	-	Calcium	5	0	4	1
Icteric index	2	2	0	-	Phosphorus	4	0	4	0

* These represent data, as available, from 51 randomly selected cases from the literature, plus 17 other cases available to the author. They do not include the data reported by Looney or the data given in the present report.

With regard to liver function, it would appear from the table that hypoalbuminemia with a compensatory globulinemia exists in these patients as expected. Also, as expected, the alkaline phosphatase is frequently elevated. Of the other liver function tests perhaps the most significantly abnormal is the bromsulphalein retention, if we recall that this test was also abnormal in otherwise asymptomatic Thorotrast recipients given in this report.

4. Blood chemistry studies

Table 2 also presents some of the blood chemistry studies done on the group of patients in this report. Nearly all are within normal limits. A review of the literature and other sources indicates that serum electrolytes and other blood chemistry studies generally become abnormal only during the terminal stages of disease produced by Thorotrast. When abnormal values have been reported these have been due to markedly depressed liver function or to some other underlying problem such as renal disease, adrenal insufficiency, malignancy or other causes.

5. Hematological studies

Leucopenia has been an inconstant finding in many Thorotrast cases. At times it has existed even when a proper stimulus (pneumonia) was felt to be present (Fruhling et al., 1956). The nature of such depression and its significance vis-a-vis the question of Thorotrast-induced leulemias and anemias is of great interest.

In an unusually large study Backer (1956) reported that Thorotrast-injected individuals had a higher frequency of abnormal blood counts than his control groups. He noted that lymphopenia appeared to be the most frequent and persistent hematological abnormality. He was unable to demonstrate any relationship between the dose of Thorotrast injected and the presence of lymphopenia.

In Table 4 there is presented a summary of hematological studies performed on the two groups of patients cited in this report. The findings were normal except for the apparent eosinophilia which appears to characterize the Michigan cases.

Eosinophilia has been noted to follow slight or moderate irradiation. The question of eosinophilia in the Michigan cases is one that will have to be explored further. Eosinophilia was not observed in the MIT cases. (This could be explained, in part, by the fact that evaluation of the Michigan patients was done by a hematologist, whereas the MIT patients were evaluated by clinical laboratory technicians.) In the series of Looney (1960), only 2 patients out of 30 had elevated eosinophil counts, and in the study of Backer (1956) no mention is made of eosinophilia.

Lymphopenia was observed in 3 of the Michigan group, while a relative lymphocytosis was observed in 4 of the Michigan group and all but one of the MIT group. Leucopenia was clearly present in patient M2, but this patient was on anticonvulsant therapy.

There is nothing obvious that can be extracted from these observations beyond the variable nature of individuals and the response of their hematopoietic systems to Thorotrast, if such be the case. In one group of patients, Fruhling et al. (1956) noted leukopenias in the presence of lymphocytosis and lymphopenia. Such observations have been recorded in a number of instances (for example, see Looney, 1960).

Table 5 gives a summary of hematological findings in a number of terminally ill Thorotrast recipients. Anemia is a prominent feature. Anemia is not a finding in the asymptomatic Thorotrast group cited in this report. In the group reported by Looney, about half the patients were either slightly or definitely anemic. Backer (1956) did not give any indication as to whether his group of patients had any problems with anemia, but Faber (1962) in referring to the same group of Thorotrast recipients from which Backer's cases were taken notes that one death due to a hemolytic anemia did occur, while three other patients in the Danish series died with aplastic anemia, myelosclerosis and agranulocytosis.

Platelet depression with and without bleeding phenomena has been reported (Fruhling et al., 1956; Gardner and Ogilvie, 1959; Finch, 1963; Okinaka et al., 1957). The group of Michigan patients discussed in this report all had normal counts. Leukemias have been described (Blomberg et al., 1963; Silva Horta et al., 1965; Netousek and Dvorak, 1957; Moeschlin et al., 1953), but the relationship to Thorotrast at times has been

Table 4

Peripheral blood studies in Thorotrast recipients

Patient Number	Retention Period (yrs.)	Hbg.	Hct.	WBC	Platelets	Reticulocyte	Neutrophils				Monocytes	Basophils	Eosinophils	Cell Morphology *
							Segmented	Non Segmented	Large Lymphs	Small Lymphs				
UM 1		10.9	34	9,000	593,000	1.5	68	16	6	3	7			Vacuolated Polys
UM 2		12.1	35.5	3,400	246,000		44	4	35	3	10	2		+A, +P
UM 3		15.3	44	9,750	250,000	0.9	48	2	31	6	9		4	+A, +P, + +T
UM 4		17.0	51	5,700	N		69	4	8	7	12			N
UM 5		14.3	44.5	12,100	254,000	1.0	45	7	16	20	2	1	9	+A, +T
UM 6		15.1	45	9,400	305,000	0.6	63	3	22	4	3		5	+A, +P
UM 7		14.6	46	9,100	N		65	9	4	9	7	1	5	+A, +P, +T
UM 8		13.7	40	4,600	N		53	1	35	9	2			+A, +P
UM 9		14.4	41	4,800	224,000	0.5	51	10	20	6	6		7	+T
UM 10		15.9	46	6,300	203,000	0.8	51	1	16	14	10		8	+A, +P
MIT 1	10		49	7,800			58		38				4	N
MIT 2	11		42	8,100			64		36					N
MIT 3	10 13		42 45	7,100 8,400			NA 39	57			1		3	N
MIT 4	17		44	5,200			67	31			1		1	N
MIT 5	26		41	9,900			57	40			1		2	N
MIT 6	NA		37	7,000			63	35			2			
MIT 7	13		39	8,200			51	39			6	2	2	

Key to Symbols

* A = anisocytosis
P = poikilocytosis
+ = slight
+ + = moderate
polys = polymorphonuclear cells
N = normal or normocytic
T = toxic granulations present in leukocytes
UM = University of Michigan Subjects
MIT = MIT Subjects

clouded by other factors, such as anticonvulsant drugs or radiation exposure (Faber, 1962). When recorded, the erythrocyte sedimentation rate has been elevated in about half the cases.

Table 5

Laboratory studies in Thorotrast recipients *

Test	Times reported	Results H	N	L
Red cells	21	2	6	13
Hematocrit	14	0	5	9
Hemoglobin	32	2	7	23
White cells	42	17	21	4
Polys	33	15	14	4
Lymphs	28	3	17	8
Platelets	16	0	9	7
Reticulocytes	3	1	2	0

* These represent data, as available, from 51 randomly selected cases from the literature, plus 17 other cases available to the author. They do not include the data reported by Looney or the data given in the present report.

. Bone marrow studies

Bone marrow biopsy is a useful adjunct in the evaluation of Thorotrast recipients (Fruhling et al., 1956). A recent paper by Finch (1963) describes 3 cases in which Thorotrast was noted in unstained preparations of bone marrow. In one of the cases, examination of the bone marrow apparently aroused suspicion of Thorotrast deposits. This was confirmed by a negative stain for iron and by X-ray. Finch states that it is possible to distinguish between Thorotrast deposits and hemosiderin in unstained marrow preparations.

Table 6 presents a summary of the bone marrow findings of the Michigan group. They are notable in two respects. First, lymphopenia is a frequent finding. Second, eosinophilia is noted. This latter finding supports the eosinophilia noted in the peripheral blood. With findings such as these, one is strongly tempted to conjecture about their meaning. Everything from radiation effects to chemical effects due to Thorotrast could certainly have to be considered. To the author's knowledge, no similar bone marrow studies in humans have been reported, although several marrow studies in symptomatic patients have appeared. It would be of great interest to expand these studies in asymptomatic Thorotrast recipients and to correlate them with experimental studies in animals.

. Chromosome studies

Because Thorotrast is deposited in lymph nodes, spleen and bone marrow, it might be expected that chromosome abnormalities produced by

Table 6

Bone marrow in Thorotrast recipients

Patient	Cellularity	E:G Ratio	Erythropoiesis	Granulopoiesis	% Eosinophils	% Lymphocytes	Megakaryocytes	Thorotrast	Impression
1	D	1:10	Normoblastic	Orderly w/slight shift	2	2	Present & budding	No	Hypoplastic and reactive w/decr. erythropoiesis and rel. granulocytic hyperplasia. (Pt. had diverticulitis.)
2	N	1:4	Normoblastic	Orderly	2	7	Present & budding	No	Normal
3	I	1:4	Normoblastic	Orderly. Inclusion bodies. Vacuolization.	8	1	Present & budding	Yes	Mod. hypercellularity w/ eosinophilia & lymphopenia.
4	I	1:3	Asynchrony w/occ. giant binucleated normoblast.	Orderly	5	1	Present & budding	No	Hyperplastic w/mod. erythrocytic dysplasia, eosinophilia and lymphopenia.
5	N	1:3	Sl. asynchrony	Orderly	3.5	0.5	Present & budding	No	Normocellular w/sl. eosinophilia & lymphopenia.
6	N	1:2	Normoblastic	Orderly	5	2	Present & budding	No	Normocellular w/eosinophilia and lymphopenia.
7	N	1:3	Increased mitotic activity. Macronormoblastic dysplasia.	Orderly	5	1	Present & budding	Yes	Normocellular w/eosinophilia and slight lymphopenia.
8	Dil	1:2	Normoblastic	Orderly	6	2	Not seen	No	Dilute specimen.
9	D	1:3	Normoblastic	Orderly	3	0.5	Present & budding	Yes	Normocellular w/rel. lymphopenia and sl. eosinophilia.
10	Dil	1:4	Normoblastic	Orderly	9	2	Not seen	No	Relative eosinophilia.

radiation could be demonstrated in the leukocytes of the peripheral blood. Persistent chromosome abnormalities have been noted following exposure to external radiation and similar abnormalities have been noted with internal emitters (Bloom and Tijo, 1964; Nofal and Beier-Waltes, 1964; Bender and Gooch, 1963).

In our laboratory chromosome studies of patients with Thorotrast burdens have begun, but our own efforts have not progressed to a point where we have any results to report. However, chromosome studies have recently been performed on a representative series of patients containing radium and Thorotrast, and I have the privilege to cite some of the results of this work which is presently being prepared for publication (Lisco, 1965).

Studies were made on leukocytes from the peripheral blood of patients who had received Thorotrast for a variety of reasons 10 - 20 years earlier. The patients were chosen for study not only to examine the effects of Thorotrast, but to compare them with radium patients on whom similar studies were being made. The two radioactive materials differ in their pattern of deposition in the body, and it seemed likely that there would be a corresponding difference in the extent of chromosome pathology.

Radiation-induced chromosome aberrations have been found in all Thorotrast patients so far examined. The nature of the aberrations is the same as that seen with other types of radiation exposure, both external and internal. In general, the frequency of aberrations is considerably higher in Thorotrast than in radium patients. Similarly, the number of aberrant chromosomes per cell is considerably higher in the former group. This finding had been anticipated because Thorotrast, in contrast to radium, is largely concentrated in macrophages of the reticuloendothelial system, the source of many of the cells that are seen dividing in short-term blood cultures.

Chromosome analysis has, in fact, proved to be a very sensitive indicator of the presence of Thorotrast in the body. In one instance where chromosome studies were made for totally unrelated reasons a history of Thorotrast injection was suspected solely on the basis of the rate and number of chromosome aberrations found. Proof of a diagnostic Thorotrast injection was later obtained from a search of the patient's record.

Next to measurement of radioactivity in the patient by whole-body counting or visualization of Thorotrast deposits on X-ray films, chromosome analysis appears to be the most sensitive diagnostic procedure available for the detection of Thorotrast in man.

5. Radiographic and other studies

The radio-opacity of Thorotrast made it a highly useful X-ray contrast medium. Its high retention by the body has made possible continued visualization of the liver, spleen and other organs into which it was injected or into which it was extravasated. X-ray diagnosis has therefore been a successful means of establishing the presence and distribution of Thorotrast. The redistribution of Thorotrast leads from a

diffuse distribution in the liver to a more reticular pattern of opacification which corresponds to the microscopic observations (Silva Horta, 1951; Thomas et al., 1951). Regional lymph nodes are frequently noted to pick up Thorotrast. In later stages, progressive fibrosis leads to a decrease in the size of the liver and spleen.

While the usual abdominal X-rays and films of the regional areas into which Thorotrast may have been extravasated generally have been adequate, tomography has also been used in situations where a more definite outline of the Thorotrast deposit is required (Dahlgren, 1961).

Liver and spleen scans following the injection of radioactive rose bengal, chromium tagged cells, or radioactive gold are used to assess the functional state of these organs as well as to demonstrate the presence of malignancy in the liver. Such investigations have sometimes been of help in Thorotrast cases also (Smith, 1965).

Since bone-seeking radionuclides such as radium are known to induce radiographically detectable changes due to radiation osteitis (Aub et al., 1952) a consideration of this possibility in Thorotrast patients has not been overlooked (Looney, 1960). The evidence would suggest that no changes comparable to those seen in radium dial painters can be found. However, efforts to improve the sensitivity of X-ray methods for assessing radiation effects are still underway and in the Thorotrast studies being sponsored by the U.S. Public Health Service, Division of Radiological Health, a careful study of the bones will be made. Time may play an important role as far as the production of any changes are concerned, and it would seem worthwhile to continue with radiographic as well as autoradiographic and microradiographic studies of the bone.

9. General discussion

In the preceding pages there has been presented a brief review of some of the clinical and laboratory findings reported for Thorotrast recipients. The relative usefulness of any of the diagnostic measures is difficult to judge because of the rather variable reporting of clinical findings which have appeared in the literature. The fairest thing that can be said is that the applicability and usefulness of any of these measures appears to be the same in the Thorotrast recipient as it is in patients with other disorders, and that in the final stages of Thorotrast effects the clinical alterations become fairly obvious.

Since Thorotrast produces chronic toxic effects it may well be that studies such as peripheral blood, bone marrow examinations, or bromsulphalein retention may provide an early clue to altered physiology in an otherwise asymptomatic patient. The question of patient management at this point would certainly be a difficult one. Beyond this, however, there are other advantages that could be derived from such early studies. It has been estimated that between 10,000 and 100,000 individuals have been injected with Thorotrast. A number are still living. These represent an unusual opportunity to assess quantitatively the toxic effects of a particular radioactive material which, in view of the irreplaceable nature of this group, will never again present itself. The value of prospective studies of such patients would certainly appear great. That

such studies can successfully be accomplished has already been demonstrated in the follow-up of former radium workers.

In such studies, the question of the usefulness of the clinical and laboratory evaluation has been raised repeatedly. It is costly and time-consuming to see these patients. There are other barriers that one encounters. There is little question, however, that a comprehensive evaluation of these patients is highly desirable because it is important to know when, as well as the manner in which the toxic agent produces its effects. Unfortunately, most clinical diagnostic methods are not very sensitive indicators of radiation damage. How useful the ordinary tests can be in foreshadowing Thorotrast effects is still a problem of interest. However, if a sufficient number of patients could be studied certain of these problems might be quickly resolved.

The difficulties in collecting this kind of information are known to all who have attempted it. It would certainly seem desirable to have some plan whereby comparable information could be obtained among those groups where Thorotrast studies are being conducted, so that questions relating to Thorotrast toxicity and dose-effects could be answered sooner or more completely. An eloquent recommendation to this effect has already been made by Marinelli (1960).

10. Summary

A review is presented of some of the clinical findings and laboratory studies for a group of relatively asymptomatic Thorotrast recipients. There is also presented a review of the altered physical and laboratory findings which have been described in the literature. The point is made that in the final stages of Thorotrast effects the clinical alterations become fairly obvious. Earlier, certain tests such as bromsulphalein retention or bone marrow abnormalities may reflect Thorotrast effects in otherwise asymptomatic patients.

It is suggested that continued study of Thorotrast recipients is worthwhile, in particular to establish possible dose-effect relationships. The difficulties in conducting such studies are noted and a suggestion is made that it would be useful to have comparability of data amongst interested groups so that questions relating to dose-effects would be more readily answered.

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CHROMOSOME STUDIES ON TWENTY PERSONS INJECTED WITH THOROTRAST

P. Fischer, E. Golob, E. Kunze-Mühl, and T. Müllner

Ed. Note: An article by Fischer et al. (1966) incorporating the material of this paper was published subsequent to this conference in a scientific journal.

Summary

1. Cultures of leucocytes from 20 persons with Thorotrast burdens and 5 persons without Thorotrast burdens have been examined. None of these patients has a history of X-ray therapy.

2. Chromosome aberrations were present in 19 of the 20 Thorotrast cases but in none of the 5 normals.

3. An attempt is being made to see whether the number of aberrations observed is correlated with the amount of Thorotrast in the body.

NEOPLASMS OF THE LIVER FOLLOWING THE DEPOSITION OF THORIUM DIOXIDE

R. L. Swarm

1. Introduction

Many individual case reports and several follow-up studies of groups of human patients have established the carcinogenic effect of thorium for man at several different sites. Although doubt about the association of neoplasia with thorium no longer exists, several interesting questions remain. Case study of patients who have thorium deposits in their tissues constitute a valuable source of information about this unique carcinogen, a radioactive material, in man. Patients of this type may soon disappear from the scene and be no longer available for study as thorium dioxide is not used in large doses or in many patients. Following the intravenous injection of thorium dioxide, the most common site for neoplasms in man is the liver. Since three types of tumors have been reported in the liver, the morphogenesis of these hepatic neoplasms is of particular interest.

2. Malignant vascular neoplasms

Spontaneous malignant vascular neoplasms (hemangioendotheliomas, Kupffer cell tumors, angiosarcomas, hemangiosarcomas) of the liver are not common in man. From the time of the early report by MacMahon et al. (1947, 1947a) to the most recent thorough report by Silva Horta et al. (1965), the majority of the malignant vascular neoplasms of the liver reported in the literature have been in patients with thorium deposits. It would appear that the number of thorium-induced, malignant, vascular tumors is greater than the number of spontaneous malignant vascular tumors of the liver.

Morphologically, the malignant vascular tumors vary in differentiation and appearance so that there is a spectrum of tumors ranging from those composed of well differentiated endothelial cells to those that are poorly differentiated vascular sarcomas. MacMahon's tumor was well differentiated with only foci of hemorrhage present grossly. No gross tumor was described. Histologic sections of the hemorrhagic areas showed well-differentiated endothelial cells surrounding and infiltrating between the liver cells adjacent to these areas. The poorly differentiated vascular tumors are grossly nodular tumors that are composed of less well-differentiated cells in which the vascular pattern may be less than clear. All the types of malignant vascular tumors seen in thorium dioxide patients may involve other sites of thorium deposition in addition to the liver, such as the spleen and bone marrow, and they may metastasize to the lung. Death due to rupture of the hepatic vascular tumor nodule and intraperitoneal hemorrhage has been observed in man (Rosenbaum, 1959).

This malignant vascular tumor is often multiple in the liver. Usually the histologic character of the different nodules is very similar. Although a multifocal origin of the vascular tumor seems reason-

able since the thorium deposits are widely scattered, evidence for this point is not clear from the review of several human tumor cases. In such experimentally induced tumors in the rabbit, separate nodules of malignant vascular tumor are occasionally of such a different character that the development of multiple primary tumors is more strongly supported (Swarm et al., 1962).

The lack of association of nodules of hemangioendothelioma with nodules of hepatoma in the same human or experimental host suggests that factors may exist in a given individual to favor the development of one type of tumor rather than the other. The quantity of thorium dioxide administered, the pattern of distribution of thorium dioxide in the phagocytic endothelial cells, the hormonal status of the host, and the extent of cicatrix about the thorium dioxide deposits are some of the factors being studied to explain different patterns of tumor morphogenesis. Two points seem clear. The malignant vascular tumors may develop in livers that contain very little cicatrix about the hepatic deposits of thorium dioxide. This is true in some human patients, and it is particularly true in experimental animals where the amount of cicatrix about thorium deposits is less in all sites. (These malignant tumors may also occur in patients with cicatrix about the sites of thorium deposition.) Scar formation is not required for the development of this tumor. Second, although the malignant vascular tumors are probably derived from phagocytic endothelium, the tumor cells are usually not phagocytic and seldom contain thorium even though this may be released into the general circulation by the extensive destruction of the liver and spleen that occurs when a rapidly growing neoplasm is present.

The etiologic relationship of thorium dioxide deposits in the liver and spleen to the subsequent development of the malignant vascular group of tumors seems clear from the rather close association in man and the high incidence of this lesion in experimental animals. The malignant vascular tumor in the rabbit is of particular significance since similar spontaneous tumors have not been seen. (Spontaneous hepatic tumors of the rabbit of all types are rare.) Yet it must be remembered that malignant vascular tumors do occur in man without thorium dioxide (Burston, 1958) and that they have also been found in patients with certain kinds of exposure to arsenic (Roth, 1957).

3. Hepatomas

Hepatic parenchymal cell tumors of the liver occur more commonly in people who have no thorium dioxide deposits than they do in patients with such deposits. Simple association of the two conditions is not suggestive of an etiologic relationship.

In the cases reported in the literature, investigators have usually evaluated their cases carefully and have reported those cases with long latent periods after thorium deposition. They have excluded the patient with a hepatoma who is given thorium. It is more difficult to exclude the patient with pre-existing hepatic disease who is given thorium dioxide. Cirrhosis, hepatitis, and other factors pre-

dispose one to hepatic parenchymal cell tumors (Gall, 1960). Some of the patients in whom thorium was used for hepatolienography had such pre-existing liver disease. Yet they often had a large dose of thorium dioxide and may be expected to have a high incidence of tumors. An altered pattern of thorium distribution may exist in the patients with pre-existing liver disease. The pattern of thorium dioxide distribution is being studied in these patients. The thorium deposits in the liver may accentuate any tendency present to form localized areas of cicatrix in the liver.

Is there something distinctive about the hepatomas that develop in patients with thorium deposits? In some cases the tumor is seen to develop in the immediate vicinity of a large focal deposit of thorium about which there is considerable cicatrix. The location of the tumor near such a cicatrix allows the investigator to suggest an etiologic relationship. Yet, it is true that chemical carcinogens which may produce cirrhosis may also induce neoplasms without cirrhosis if the dose and diet are altered. Careful morphologic study of thorium dioxide patients who die with intercurrent disease may reveal small hepatic tumors. Study of these may facilitate a better understanding of their morphogenesis. In late cases with extensive tumor involvement, it may be difficult to relate the site of origin of the tumor to a thorium deposit even if this is the case.

In addition to the study of human cases, evidence that hepatomas may be caused by thorium dioxide deposits comes from certain experimental studies in which tumors of this type have been produced in rodents (Guimaraes et al., 1955; Guimaraes and Lamerton, 1956; Bensted and Crookall, 1963; Grampa, 1965). On the other hand, in rabbits, an animal with a longer life span, only the malignant vascular tumors have been seen.

4. Adenocarcinomas of bile duct type

The etiologic relationship is often hard to establish in cases of adenocarcinoma in thorium patients. Yet cases do exist in which tumors have developed just beneath the liver capsule near subcapsular deposits of thorium. One of the cases reported by Gardner and Ogilvie (1959) may be an example of this. Another case had tumor limited to the subcapsular location where thorium deposits are regularly found in patients with a latent period of several years after the administration of thorium dioxide (Swarm, unpublished).

In other sites such as the maxillary sinus, the kidney and the breast, thorium dioxide deposits in prolonged contact with the epithelium are sufficient to induce carcinomas. Contact with the epithelium for long periods may be the common factor in carcinoma cases. In sites of exposure where prolonged contact with the epithelium is not maintained, such as the gastro-intestinal tract, no tumors are known to exist.

5. Localized malignant lymphomas

Virtually non-existent in the liver, spleen and abdominal lymph nodes of thorium patients are such tumors as reticulum cell sarcoma and lymphosarcoma. These tumors are absent despite the destruction of lymphocytes, and extensive fibrosis occurs often in the spleen and upper abdominal lymph nodes. The production of leukemia or lymphosarcoma may be more closely related to widespread or generalized injury of the bone marrow and lymphocytic structures than it is to the local necrosis and scarring of regional lymph nodes in one area. Extensive loss of lymphocytes and cicatrix formation regularly occurs in the lymph nodes near the liver and spleen in the upper abdomen after thorium dioxide reaches these lymph nodes. One possible case that may be related to this is a case of abdominal Hodgkins disease (Verner and Smith, 1963).

6. Summary

Tumors of the liver most commonly seen in thorium dioxide patients are the malignant vascular tumors. These are probably caused by the thorium deposited in the tissues of the liver, spleen and bone marrow, the organs involved. Some hepatomas and adenocarcinomas of the bile duct type are located near thorium deposits in the liver. An examination of the morphogenesis of these tumors in well studied human cases and experimental animals may lead to a better understanding of factors which determine the type of tumor that develops in man after hepatic injury.

THOROTRAST INDUCED FIBROSIS*

J. da Silva Horta

Most authors who have investigated the effects of Thorotrast in man, with the exception of some workers such as Brünner (1960), show more interest in its carciogenic effect and its possible action on the bone-marrow (leukemias, pancytopenias and purpuras) than in its fibrotic effect. We have given our attention also to fibrosis. When Thorotrast is deposited at any site in the human body, there is always neoformation of fibrous tissue. This fibrous neoformation is expressed in our cases by granulomata, liver fibrosis, spleen fibrosis, and fibrosis of the tributary lymph nodes of the liver and spleen, and by renal scar tissue in retrograde pyelography. We shall not discuss now whether the fibrous proliferation is produced by the radiation emitted. This fibrosis can lead to death as in the case of granulomata (death by asphyxia due to bilateral recurrent nerve paralysis, etc.) or by liver insufficiency and portal hypertension in the case of liver fibrosis. Its presence can also lead to other symptoms which will be referred to later. We should not forget, too, that malignant neoplasms can develop around large deposits of Thorotrast (four in our series).

1. Thorotrast granulomata

1.1 Definition and classification

By the term "Thorotrast granuloma" we mean the tumor-like mass of fibrous tissue originating at the site of an extra-vascular Thorotrast deposit. We may classify the Thorotrast granulomata in the following way:

(1) Perivascular granulomata;

(2) Pericanalicular granulomata (retrograde pyelography, dacryocystography, mammography, etc.);

(3) Intracavitary granulomata (natural cavities such as the facial sinuses, the joint spaces; and pathological cavities such as fistulas, cerebral abscesses after emptying);

(4) Visceral granulomata such as those of the lung and the liver.

1.2 Case material

Our survey has included 85 cases of "granulomata" (Table 1), 16 of which have been studied histologically (Table 2). In addition, we have examined histologically another 12 cases having extravasated Thorotrast

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* This work was carried out with the support of the U.S. Public Health Service, Division of Radiological Health, Grant No. RH-0039. This paper describes only our own experience with Thorotrast, and even that not in its entirety. We are preparing more formal publications on each of several topics: Thorotrast granulomata; fibrosis of the liver, spleen, and lymph nodes; neoplasms; and bone marrow diseases. These will contain more complete references to the literature.

Table 1

Thorotrast granulomata cases

	Cervical	Non-cervical
No. of cases		
Unilateral	51	18
Bilateral	14	2
Total	65	20
Death from granuloma	10	2
Malignant neoplasm at edge of granuloma	2	2

at the site of injection but not showing granulomata. These latter 12 cases received Thorotrast for cerebral angiography (9), retrograde pyelography (2), and mammography (1) at a time one day to two years before the histological examination.

1.3 Summary of symptoms

The symptoms, which result from compression and destruction of structures where Thorotrast is deposited, vary greatly according to the site and extent of the granuloma. In all cases spontaneous pain is a common symptom. In cases with retrograde pyelography, in whom the contrast medium passed to the renal hilum, pain was the only symptom. In one case with granuloma of the elbow fold (hepatosplenography), in addition to pain there was difficulty in moving the elbow joint. In cases in whom arthrographies were made, limitation in the movements of both the knee and the elbow joint was also observed. Fistula with a possible ultimate infection is not a common finding in our series. One patient with cerebral granuloma had to be operated upon 5 years after an injection of Thorotrast into the cavity of the drained abscess for periodic control of the cavity size, due to the onset of epilectic seizures. We have greater experience with "neck granulomata". Besides the spontaneous local pain and that brought about by the head movements, pain along the arm and also other varied and severe symptoms were complained of by these cases. Dysphonia is very frequent. We have cases with dyspnea and asphyxia (5 cases - bilateral granulomata), dysphagia, tongue atrophy, pharyngeal ulcers, eyelid ptosis, a complete Claude Bernard - Horner syndrome, ulceration to the exterior with hemorrhage (one fatal case) and a left chylothorax by compression of the terminal part of the thoracic duct. We also observed local muscular contraction. A combination of two or more of these symptoms can be found in the same patient, the most frequent being pain, difficulty in the movements of the head, dysphonia, dyspnea, and dysphagia.

1.4 Pathology

Our histologic examinations gave an understanding of the histogenesis of the granuloma and the charges represented by the disintegration of newly formed collagen which makes up the granuloma tissue. Histological, histo-

Table 2

Granulomata cases

Case	Source of tissue	Route of injection	Time elapsed since injection (yr)	Granulomata symptoms
1	Nephrectomy of the remaining kidney	Retrograde pyelography	5	Present
2	Excision of the neck granuloma	Cerebral angiography	5	"
3	Excision of the granuloma (brain)	Injection into the cavity of the cerebral abscess	5	"
4	Excision of the leg granuloma	Injection for sclerosis of the varix	13	"
5	Excision of the knee granuloma	Arthrography	14	"
6	Autopsy	Cerebral angiography	14	Absent
7	Excision of the elbow fold granuloma	Hepatosplenography	17	Present
8	Biopsy of the neck granuloma	Cerebral angiography	19	"
9	Autopsy. Granuloma of the elbow fold	Hepatosplenography	21	"
10	Autopsy	Cerebral angiography	24	"
11	Biopsy of the neck granuloma	" "	25	"
12	Autopsy	" "	28	"
13	"	Portography	28	Absent
14	"	Cerebral angiography	28	"
15	"	" "	30	"
16	"	" "	31	Present

chemical and chemical (detection of proline and hydroxyproline) methods were employed in this study.

A completely formed granuloma consists of hyalinized dense connective tissue. The hyalinization is precocious and vascularization is as a rule poor. Fibrosis and calcification of the hyalinized tissue render the granuloma hard. This fibrous tissue has an important invasive characteristic, making the separation of the Thorotrast granuloma from the surrounding structures difficult. As a result of this we observe, especially in granulomata of the neck, compression and destruction of muscles, cranial nerves (IX and XII), the recurrent laryngeal nerve, the brachial plexus, the cervical sympathetic chain, the carotid artery, the jugular vein, and even the aortic arch. This explains the clinical findings mentioned above as well as their variability. These neck granulomata often extend from the base of the skull down to the arch of the aorta, or to the contralateral side making a prominence into the pharynx or compressing the esophagus.

Our various cases show that fibrosis is found very early (even at 24 hours). There is no granulation tissue. (Therefore the term "granuloma" is improper - the terms "contrastoma" and "Thorotrastoma" are worse still.) The deposition of Thorotrast granules induces a histiocytic proliferation which is proportional to the amount of the material extravasated. The histiocytes containing Thorotrast (Thorotrastophages) can be seen within a few hours, along with the first proliferated fibroblasts and the newly formed collagen fibers which are positive with Van Gieson stain. The extracellular granules are those still not phagocytized and those eliminated from the dead histiocytes. The presence of Thorotrast deposits, and increased numbers of histiocytes, fibroblasts, and newly formed collagen fibers, are all features of the granuloma.

The histiocytes which take part in this process belong to the region where Thorotrast id deposited. In the case of neck granulomata those which are found within the sheath of the neuro-vascular bundle of the neck are involved. When Thorotrast at injection reaches other structures, such as adipose tissue, muscle, etc., the histiocytes of these structures are involved.

The collagen tissue undergoes important changes with time. First there is hyalinization, then calcification which is sometimes very extensive, appearing at regions with or without fibrinoid degeneration, and finally there is softening. These changes observed at older sites of the granuloma are associated with the death of the cells of these regions. Thorotrast is then seen in the free state, but much of it is gradually phagocytized by the histiocytes of the surrounding regions. Here once again fibroblast proliferation and neoformation of collagen fibers occurs and in this way the granuloma extends beyond the regions where Thorotrast was initially deposited. This is what we call the "growing zone" or "proliferating zone" of the granuloma.

The extent of the granuloma depends on the extension of the initial Thorotrast deposits. Transport can explain the presence of this material at distant sites, for example at the base of the skull and at the opposite side. We are also convinced that gravity plays an important role in its downward progression (as far as the aorta, for example).

The degradation and softening of collagen is a common finding in older granulomata. Grossly this softening can be represented as cystic formations full of a "gelatinous" substance. Microscopically the collagen loses its normal histologic characteristics, transforming into an amorphous mass, sometimes calcified, wherein calcium granules can be seen mixed with Thorotrast and small blocks of collagen and cholesterol crystals. In addition, the collagen tissue loses its histological and histochemical properties. We studied the amino acid composition of the altered collagen in three of the granulomata and verified that hydroxyproline did not exist.

The softening of the collagen tissue largely explains the fistulas that can develop through the skin to the exterior or through the mucosa of the pharynx into its cavity. When a softened zone establishes a communication between the lumen of the carotid artery and the exterior, hemorrhage may occur. This hemmorhage proved fatal in one of our cases.

The appearance of the granuloma has been described at length. Is it merely a foreign body type of reaction to the presence of Thorotrast granules? Is it a reaction to a heavy metal? Is it due to the presence of dextrine? Does radiation take an active part in the process? In any case, however, it is not customary to see such severe disintegration of the collagen tissue in very old fibrosis, such as in keloid and in mammary dysplasia. Rundo (1957) found thorium daughter products in a case of Thorotrast granuloma and he attributes the fact to poor vascularization of this tissue. Probably in this severe disintegrating process the radiation plays an important role.

As regards Thorotrast, and most probably as regards other substances too, we have to consider the animal species into which the substance is injected. The human species is particularly sensitive to the sclerosing action of Thorotrast. Experiments conducted in different animal species have not yielded identical degrees of fibrosis. Practically all these investigations concern liver fibrosis. It seems that rabbits are less susceptible than rats and mice. In work as yet unpublished we obtained in livers of rabbits just a little portal fibrosis 2 years after the injection of Thorotrast in doses per kilogram of body weight similar to those employed in man for hepatosplenography. Also injections of Thorotrast into the pericarotid tissues of rabbits did not induce Thorotrast granulomata within two years of injection.

Our radiation measurements of the granulomata were meant only to show that the referred specimens were impregnated with a radioactive substance.

2. Spleen fibrosis

In practically all the cases in which Thorotrast is injected into the blood stream it accumulates, with the passage of time, more in the spleen than in other reticuloendothelial organs. At first its accumulation is diffuse; it is engulfed by the reticular cells and by the cells lining the sinuses. These macrophages are small. Later Thorotrast is seen inside big macrophages, and in the spaces limited by the reticulum fibers. This accumulation occurs in clumps and always at the same sites, namely around the arterioles (sometimes following very closely their branchings), around big arteries, and at the borders of the trabeculae. At this stage

its distribution is nonuniform. A continuous gradation between these two stages can be observed, and even in those cases in which the distribution in clumps is well established there are always a few big or small Thorotrastophages free in the pulp.

Thorotrast can be seen very early in the trabeculae of the spleen, especially in those which converge to the hilum of the organ. The other trabeculae which "insert" directly on the capsule far from the hilum seldom contain Thorotrastophages. The capsule can also contain thorium inside small macrophages. However, in the spleen there is not, as in the liver, a movement in the direction of the capsule which confers on the external surface of the liver at gross examination such a characteristic appearance. Usually the external surface of the spleen is white due to the fibrous thickening as will be referred to further on.

Groups of Thorotrastophages are found dispersed in the pulp, very often inside the "blood-lakes" which when observed under low power look like hemorrhagic areas. The Mallory staining techniques and the silver staining method show that these areas are cavities limited by precollagenous fibers. They contain erythrocytes and hemosiderophages, but no other cell except an occasional pyknotic nucleus. At these sites the reticulum fibers are very often fragmented and may even disappear completely. Since these areas are extensive it is impossible to recognize in them the Billroth cords, the sinuses, and the Malpighian corpuscles. On the contrary, some fibers are thickened. What has been described above is also true with regard to accumulation of Thorotrastophages without erythrocytes. This destruction of the cells is a rule. Sometimes there are larger zones changed into a network of very fine reticulum fibers with a few cells reduced to their pyknotic nuclei. This occurs above all at sites where Thorotrast accumulates in smaller amounts, as for example at the subcapsular region.

From the changes mentioned above there is a collapse which gives the capsule a wavy aspect. Later fibrous tissue appears, first at the bottom of the capsular depression, second all around the organ. In very old cases this tissue is of great thickness, being made up of collagen tissue and very few cells. It is practically always possible to distinguish it from the capsule with any staining technique, but above all with elastin since the capsule remains rich in elastic fibers while the newly formed tissue, situated on the outside of the capsule, has no elastic fibers. Due to collapse the trabeculae come in contact with each other, thus giving an erroneous appearance of greater thickness of the trabeculae. With time the collagen and the precollagen fibers of the pulp appear and constantly increase. It is a very irregular fibrosis without elastosis.

We can thus understand that the spleen, due to this collapse, is greatly reduced in size - 4 to 4.5 cm in its greatest diameter. These spleens have of their original structure just the trabeculae and the capsule left, the rest being free Thorotrast, collagen and precollagen fibers.

In many of our cases the older collagen underwent the changes described in granulomata, namely hyalinization, increased eosinophilia, PAS positive areas, and calcification. The calcification is sometimes very extensive. We did not encounter, however, the softening with disintegration described by us as occurring in granulomata. However, we would like to mention the following points:

(1) We do not know the reason why the spleens of cases with the same number of years of evolution and injected with the same quantity of the contrast material differ sometimes in their volumes.

(2) One interesting point is the considerable number of plasmocytes observed in some cases in the vicinity of Thorotrast deposits.

(3) Another interesting point is the existence of fibrinoid material, which in one of the cases was very conspicuous. Some of these cases also had some fibrinoid material in the bone marrow. The coexistence of fibrinoid material and plasmocytes is also not infrequent. In some cases the "fibrin" forms a band between the more or less normal tissue and the large deposits of Thorotrast, and still this band of "fibrin" can be seen between the great accumulation of Thorotrastophages and plasmocytes. Obviously these aspects which we have described can be observed only in those organs which have their structure still somewhat maintained, above all in those without serious fibrosis.

(4) We would still like to make reference to the epithelioid nodules described by our collaborator Levy (1960) and also ourselves (Silva Horta, 1958).

(5) Finally, there are cases in which there is follicular hyperplasia during the first years and others still in which besides this hyperplasia there is also a certain amount of fibrosis.

For these findings, immunohistological problems arise which will certainly have interest. In our follow-up we are at present very interested in studying the serum protein fractions (by electrophoresis).

3. Fibrosis of lymph nodes

In the prehension of Thorotrast by the human reticuloendothelial system the spleen is followed by the liver and the bone marrow. The lymph nodes, with the exception of those that are tributaries of the afferent lymphatic circulation of the liver and spleen (the great accumulating organs), have little Thorotrast and so practically no lesions occur in them due to its presence. The same cannot be said of the lymph nodes of the splenic hilum, splenic chain, liver hilum, and mediastinum (especially the retrosternum lymph nodes). Naturally from these lymph nodes other neighboring ones can be involved. The elimination of Thorotrast from the spleen and liver by the lymphatic circulation occurs very quickly and a great amount of this material can be seen very early in the lymph nodes mentioned.

Practically the same processes as observed in the spleen also occur in these organs, but here the distribution is as a rule diffuse. Fibrosis results very early with previous disappearance of its normal structure. The collagen tissue undergoes the same changes. The Thorotrastophages very rarely pass across the capsule of the lymph nodes.

An important point to mention is the rapidity with which the lymph nodes of the hilum of the liver and spleen become visualized, as well as the intensity of this visualization. These effects are not always pro-

portional to the quantity of Thorotrast in the main accumulating organs. In fact, the intensity of the visualization sometimes seems to be precisely the inverse, most probably due to the great rapidity of elimination of Thorotrast through the afferent lymphatic circulation.

Fibrinoid material, plasmocytes, epithelioid nodules, and the already mentioned tissue changes, including calcification, can be observed in the tributary lymph nodes. On this point the lymph nodes behave like the spleen.

4. Liver fibrosis

Our material, obtained from autopsies of individuals three years after they received Thorotrast by injection, is not entirely uniform. These studies were made more than twenty years ago and not always with the finality we presently have. While the material has been reexamined, there are points which still have to be studied in more detail. Our description of liver lesions is based on the cases included in Table 3. Our interpretation of the histogenesis is subject to correction; however, we think that the main lines have been drawn.

4.1 Gross features

The severity and the rate of development of the hepatic lesions depend on the amount of Thorotrast the liver contains. Thus we have cases with minimal lesions despite their having been injected 20 or more years back. On the other hand, a case who died 6 months after the last injection, and who had received during a period of a year and a half at least 125 ml of the material, showed very severe cellular lesions with numerous and extensive scars. A great number of the cases studied by us are of cerebral arteriography and some of these retained a significant fraction of the injected substance in the soft tissues around the carotid artery. Thus some cases, despite long retention of Thorotrast, show upon morphologic examination only a few hepatic scars. When interpreting each case we take into consideration not only the amount of Thorotrast injected but also the existence or not of local deposits and Thorotrast granulomata at the site of injection.

The gross examination of the liver of an old case (more than 20 years since the injection) in whom a large amount of Thorotrast was injected systemically showed typical results. The organ was much reduced in volume. Its external surface had depressed smooth areas of a very light yellow color due to the presence of striae as if drawn by a pen. These corresponded to deposits of Thorotrast. Generally speaking this liver could be considered identical to some cases of post-necrotic cirrhosis (cirrhosis of large nodules, hyperplasia of Marchand). The organ was so hard that it was difficult to cut with a knife. Fibrous striae could be seen on the cut surface, sometimes very regularly arranged like branches of a tree, and corresponding to the branchings of the bilio-portal spaces. The hepatic parenchyma occupied the spaces between these striae giving a pseudolobular aspect. In two cases this pseudolobulation was so marked that we are not certain it was caused by the Thorotrast. In those cases in which the amount injected is small or in whom the time elapsed since the injection is short, the liver may not be reduced in volume but has a

Table 3

Material used for the histological study of liver fibrosis caused by Thorotrast

Cases	Type of examination*	Time elapsed between administration and examination (yr)	Quantity administered (ml)	Granuloma
1	A	5	20	No
2	A	5	20	No
3	A	9	16	No
4	A	12	36	No
5	B	12	?	No
6	A	14	20	Yes
7	A	15	20	No
8	B	17	24	No
9	A	18	30	Yes
10	B	18	54	Yes
11	A	20	20	No
12	A	20	20	No
13	B	20	?	No
14	A	21	?	Yes
15	A	22	74	No
16	A	23	14	No
17	A	23	?	No
18	B	23	40	No
19	A	24	54	Yes
20	B	24	36	No
21	A	25	36	No
22	A	25	?	Yes
23	B	25	32	No
24	A	27	60	No
25	B	27	30	No
26	A	28	20	No
27	A	28	20	Yes
28	A	28	60	Yes
29	A	29	36	Yes
30	A	30	?	No
31	A	30	78	No
32	A	30	18	Yes
33	B	30	60	No
34	A	31	36	Yes
35	A	31	60	Yes

* A = autopsy, B = biopsy

very typical aspect well known to those who have experience in the matter. The external surface shows the capsule marked by light yellow striae as if drawn by a pen.

4.2 Microscopic features

We first summarize the microscopic findings and then give our interpretation of the histogenesis.

(1) Sites at which Thorotrast accumulates: The substance accumulates at certain sites, especially at the scars, either free or inside the macrophages. These sites are namely the bilio-portal spaces, the subcapsular region, around the central vein and the veins of the hepatic system, and on the walls of these veins. Grossly its presence can be noted as yellow striae under the intima of the big hepatic veins. However old the case may be, it is always possible to see some isolated Kupffer cells containing this substance.

(2) Regressive changes: The most common is atrophy of the liver cells. This is observed above all in the vicinity of Thorotrast deposits and is very severe at the immediate contact with the scars. Regressive changes occur preferentially in the bilio-portal spaces, around the branchings of the hepatic vein beginning by the central vein and also under the Glisson's capsule. As in very old cases the scars at various points anastomose, cellular atrophy being present at various sites. Atrophy is accompanied very often by distrabeculation and cellular dissociation. At the respective sites the structures become more or less loose. We want to stress that cellular atrophy is more frequent at the centrolobular region for reasons which will be explained later. In this way an "inverted lobular" image can originate. Regions of necrobiosis or isolated cells which have lost their tinctorial affinity with their nuclei in chromatolysis and pyknosis can be found together with atrophied cells. In two cases we encountered hyaline bodies similar to the Councilman bodies in cellular elements belonging to the completely dissociated cell regions. The cells with the Councilman bodies are much bigger than normal liver cells. Occasionally we saw entirely necrosed regions in the midst of a circle composed of scar tissue containing Thorotrast.

In the majority of the microscopic fields, except in the very severe cases, the reticular framework is maintained, but at the regions where cellular dissociation and necrobiosis exists the reticular fibers are fragmented and they not infrequently disappear. When the walls of the hepatic veins have a lot of Thorotrast in them their elastic fibers also fragment and even disappear. Sometimes there is in addition a somewhat fatty degeneration, but as it is obvious its dependence on Thorotrast action is disputable.

(3) Scars: As already mentioned, the scars form at sites where Thorotrast stagnates. The most important sites are at the bilio-portal spaces, subcapsular, at the central veins and at the branchings of the hepatic veins. The subcapsular scars continue with those of the bilio-portal spaces and hepatic veins at regions where these structures continue with the capsular tissue. On section the subcapsular scars are often triangular with the base turned to the exterior. The historadiographs show better the high concentrations of Thorotrast as well as the situation and correlations between the scars. The collagen of the scar tissue can become hyalinized, turn PAS positive, and even become slightly softened.

However, the severe changes observed in Thorotrast granuloma or in spleens, such as calcifications, presence of cholesterol crystals and "gelatiniform" changes, are not observed. There is no neoformation of elastic fibers in the scar tissue.

(4) Changes of the Glisson's capsule: There are cases in which the Glisson's capsule shows no other changes than the presence of macrophages with Thorotrast. In many cases, however, the capsule has a wavy aspect, and in some cases the damage is so severe that isolated pieces of the capsule appear in the midst of the subcapsular liver tissue. Not infrequently newly formed fibrous tissue can be seen over the capsule, on the external surface of the spleen, and this explains the smooth areas observed on its external surface.

(5) Biliary stasis: In some cases liver cells with biliary pigment as well as biliary cylinders and bile ducts of various diameters full of bile can be seen. In other cases there are areas of biliary necrosis at the periphery of the lobules. Sometimes perilobular fibrosis is observed.

(6) Reactional processes: Lymphocytes and plasma cells are very rarely seen either inside the lobules or in the scar tissue. However, in one case we found a lymphoreticular infiltrate somewhat polymorphous and extensive. We would however like to make a special mention of two findings. One of them, observed in some cases, is the focal intralobular cellular proliferation which we think consists of Kupffer cells. The other, also observed by us in the spleen and lymph nodes of the splenic hilum, is the presence of rather well marked nodules of epithelioid cells. These nodules are found not only in the portal spaces but also, although more rarely, inside the lobules. The cellular elements of the latter closely resemble Kupffer cells but some even gather around liver cells. The intralobular nodules separate the liver cells from each other.

(7) Regenerative processes: Among the most important regenerative processes we have the neoformation of pseudo-tubuli, some of large dimensions. There are cases in which this neoformation in the scars at the portal spaces of various dimensions has an adenomatoid appearance even showing invasive characteristics. Once we encountered not a proliferation of pseudo-tubuli but of real biliary canaliculi. We also observed, although rarely, nuclear proliferations and swelling in the bile canaliculus.

It is uncommon to see regenerative liver cells. Binucleated cells can be seen in some places with large nuclei or nucleoli. Except for the two cases mentioned already, pseudolobules such as those found in cirrhosis are not encountered. Undoubtedly, however, the great number of cells occupying vast areas between regions that have undergone atrophy take up a pseudolobular aspect. We shall discuss in detail this point when dealing with the histogenesis.

4.3 Histogenesis of liver fibrosis

When Thorotrast is systemically injected into the human body it accumulates in organs containing reticular cells. The peripheral lymph nodes even after many years have very little Thorotrast in them. However, the removal of Thorotrast from the liver and spleen by the afferent

lymphatic circulation is so quick that after a few days the sinuses of the lymph nodes of the hepatic hilum are laden with this substance. These studies will be mentioned in future publications.

Thorotrast is found, during the first days, diffusely distributed throughout the liver, having been taken up by the Kupffer cells. Part of the substance enters the blood stream again after liberation from these cells, most probably upon their death. With the passage of time the Kupffer cells containing Thorotrast gradually increase in number and accumulations of Thorotrast are less diffuse, that is, they are denser at the inner third of the lobule. As we have already described in other papers, big symplasma containing Thorotrast, developed from the Kupffer cells, are liberated and embolize the sinusoids of the inner portion of the lobule and even the central vein. These groups of Thorotrastophages are separated from each other only by reticular fibers, some of which later fragment and disappear. In the meantime, liver cells at these accumulating sites necrose and disappear. It is then that swollen reticular fibers also appear and new fibers are formed, engulfing Thorotrast. In this way the first scar tissue is just reticular in nature, giving later the Mallory and the Van Gieson reactions.

Within the first months Thorotrast can be seen in the wall of the sub-lobular and hepatic veins of various diameters. What dominates the histological picture, when various cases are studied at different times, is the centripetal movement of Thorotrast. During the first weeks and months the amount of Thorotrast in the portal spaces is minimal. We cannot deny that Thorotrast inside the Kupffer cells at the periphery of the lobule cannot be phagocytized by histiocytes of the portal spaces, or that free Thorotrast particles can move along the Disse space in the centrifugal direction to the lymphatics of the portal spaces. However, this cannot be observed with light microscopy.

The centripetal movement of Thorotrast, on the other hand, is very clear, and large quantities can be found during the first months in the walls of the hepatic veins. This proves that the lymphatics of the hepatic veins participate in this process to a considerable extent. Already in the first hours the amount of Thorotrast in the sinuses of the hilar lymph nodes is great, and these lymph nodes are always the ones which with the passage of time receive more Thorotrast (as autopsies and radiographs prove). We are thus forced to admit that a great amount of Thorotrast that started entering by the lymphatic spaces of the hepatic veins passes to the lymphatics of the portal spaces. The possibility that Thorotrast follows this afferent route is much greater, and the anatomical communications so frequently observed between adventitias of the larger hepatic veins and the portal spaces of various sizes permit us to conjecture on the existence of what we have called the "lymphatic short-circuits" between these two routes. Within a few months the amount of Thorotrast in the portal spaces gradually increases, as can be easily understood from our above conjecture.

<u>The movement of Thorotrast in the centripetal direction, either towards the lumen of the central vein (by the blood-stream) or towards the sources of the hepatic vein lymphatic circulation passing by the afferent route of the liver hilum, determine the morphologic picture of fibrosis produced by Thorotrast.</u>

Thorotrast converges to the central vein, remaining in very close contact with it during a period of time. It can thus be easily understood that this is one of the sites where the atrophying and necrotizing actions of this contrast medium are greatest. In specimens embedded in paraffin these regions correspond to looser areas and to clefts which can even be seen upon macroscopic examination of the slides. They have the appearance of "false pseudolobules". We found this aspect dominant 10 to 15 years after injection of 20 to 30 ml of Thorotrast into the blood-stream for cerebral arteriography. When these regions are observed with the silver staining method the "clefts" are seen to correspond either to dilated Disse spaces with capillary collapse or to "ex-vacuo" dilatation of the capillaries. The liver cells here are very small and many must have actually disappeared. Later, similar regions form around big scars.

The disappearance and atropy of a great number of liver cells, a process which develops very slowly, is the cause of the collapse which brings about the curling of the Glisson's capsule. Evidently retraction of the cicatricial tissue at various points of the capsule also contributes to give this aspect, but certainly to a lesser degree.

As in the spleen, for morphogenetic reasons unknown to us, newly formed fibrous tissue appears at the bottom of the capsular depression. This fibrous tissue gradually increases, producing extensive thickenings which impart to certain regions of the external surface of the capsule a smooth appearance.

Another point has still to be referred to in relation to the histogenesis of liver fibrosis, namely the disturbance of the deep lymphatic circulation of the liver. Thorotrast is eliminated from the liver by the blood-stream, part being retained in the spleen, but a part being returned to the liver following the routes already described. The amount of Thorotrast which follows the afferent lymphatic circulation is very great and as the years pass the respective lymph nodes get filled with thorium and become impermeable due to the production of collagen tissue. As a result there is a slowing and even stopping of the intrahepatic lymphatic circulation at certain regions on one side, and a modification in the normal direction of the lymphatic circulation on the other.

The next step is the formation of more extensive scars. Thorotrast particles are engulfed by the histiocytes, and as in granulomata they migrate. As can be deduced from the importance of the afferent lymphatic circulation to the hilar lymph nodes, the most important scars are those of the portal spaces. That is why the Thorotrast induced fibrosis is of the type of "pipe-system fibrosis" of Symmers.

The large subcapsular scars containing thorium make us think of the existence of communications between the deep and the superficial (capsular) lymphatic circulation of the liver. It is probable that the superficial lymphatic circulation follows its normal direction of flow to the interior of the organ, but this direction can change due to blockage of the lymph nodes of the hilum as a result of fibrosis, producing thus a great increase in the lymphatic pressure. It is probable that the capsular lymphatics establish a communication between the portal lymphatics and those leaving the liver ligaments but they too have the physiological direction of drainage from the periphery to the interior, that is, in the direction of the lymphatics which drain to the hilum lymph nodes.

In any case it is a morphologic reality that Thorotrast moves in the direction of the capsule following above all the bilio-portal septa. It is around the scars in the bilio-portal and subcapsular spaces that the most severe liver parenchymal changes are observed such as lobular distortion, cellular dissociation, atrophy, necrosis, and intercellular fibrous proliferation.

Additional histologic aspects must be briefly explained. Biliary stasis results from ductal compression by the scars, leading to loss of communication between the intralobular and extralobular biliary ducts.

The presence of pseudo-tubuli needs no explanation. We shall only draw attention to certain tumor-like appearances which may be similar to cholangiomas mentioned by certain other authors. We ourselves have an interesting example of this type.

One of our doubts is whether the pseudo-lobules sometimes observed indicate the existence of cirrhosis. We think that at least in two of our cases they do. In one case the liver strongly resembled the Marchand type of cirrhosis; prior to the patient's death a huge prominence on the external surface of the liver had been considered a neoplasm. In these cases we can speak of "Thorotrastcirrhosis".

It should be known, however, that in most cases, even in those who were injected with Thorotrast many years previously, a large part of the liver parenchyma is intact despite the lesions already described. Therefore we should not be surprised if functional disturbances do not arise. In many cases the liver has relatively little Thorotrast while the spleen becomes the chief deposit. It is not yet known why the liver under identical conditions (quantity injected, time elapsed since injection) can behave differently as regards the severity of lesions. In some cases the lesions are so severe that consequences similar to cirrhosis result.

We must speak still of the somewhat nodular proliferations of epithelioid cells. In the first place we have to exclude other diseases such as sarcoidosis even if some intralobular areas seem to correspond to simple tuberculoid granulomata. In addition to the cases published by our collaborator Levy, we have found this type of proliferation in three patients. One of these received more than 125 ml of Thorotrast by injection. Rotter thought that these nodular proliferations could be precursors of hemangioendotheliomata. Especially in two of our cases there was in fact a certain degree of similarity between these intralobular proliferations and hemangioendotheliomata. In one, this was noted in a biopsy and not at autopsy. Our epidemiological survey revealed that this patient is still alive after the elapse of 7 years.

We think that these nodules encountered in the spleen and liver and occasionally in the lymph nodes of the splenic hilum, the fibrinoid material of the spleen, lymph nodes and bone-marrow, and the great number of plasma cells appearing concomitantly in the spleen, represent a special immunological state induced by Thorotrast.

THOROTRAST PATHOGENESIS - RADIATION OR OTHERWISE?

J.P.M. Bensted

It has frequently been suggested that the carcinogenic properties of Thorotrast might not necessarily be related to its radioactivity (Faber, 1962; Looney, 1960; Guimaraes and Lamerton, 1956). It is therefore the purpose of this short review to examine some of the evidence which might account for the carcinogenic properties of Thorotrast in terms other than its radioactivity. Before discussing these possibilities in detail it might be well to enumerate some of the observations which are peculiar to Thorotrast-induced tumours in man, in the hope that some clues may arise which could throw light on the pathogenesis of these tumours.

First of all, the tumour site. It is generally agreed that most of the tumours which arise following intravascular injection of Thorotrast are either liver tumours or leukaemias (Silva Horta et al., 1965; Suckow et al., 1961; Faber, 1962; Looney et al., 1960). Among liver tumours there is an unusually high incidence of a rare mesodermal tumour, the haemangio-endothelioma or Kupffer-cell sarcoma, which has been regarded by Looney et al. (1960) as being "Thorotrast specific". Silva Horta et al. (1965) point out that 6 of the 8 leukaemias which his group studied were of an acute myeloid form which is more typical of a radiation-induced type of leukaemia. Following extravascular or intracavitary injection, the tumours are related to the tissues at the site of injection. In the case of perivascular deposits it is common to find granulomatous masses termed "Thorotrastomas" which may be associated with local fibrosarcomata.

Is it possible, therefore, to detect a single thread which may connect these apparently unconnected observations? It is, indeed, intellectually more satisfying to try to find a common thread but in fact, since Thorotrast is not a simple substance, more than one thread may be involved.

First of all, can we reconcile the fact that most of the tumours appear in the liver (rather than the spleen) with the observation that it is in the spleen that the uptake of Thorotrast in terms of mg/gm tissue is highest. Suckow et al. (1961) discuss this point and put forward three possible solutions. The first argues that the radiation dose to the liver is within the range of maximum tumour response, whereas in the case of the spleen the response is on the descending slope of the dose-response curve. Their second line of reasoning involves the concept of pre-existing tissue damage with subsequent tumour formation in that same organ. In the human material it is not fully clear to what extent the undoubted cirrhotic and fibrotic changes are post hoc or propter hoc. In experimental studies (Guimaraes et al., 1955; Swarm et al., 1962; Bensted and Crookall, 1963) there is no evidence which indicates an association between liver damage and tumour formation. The third line of argument of Suckow et al. invokes the concept of a non-uniform distribution of the radiation dose within the liver and spleen and coupled with this, the

significance of the number of cells at risk which, they argue, is greater in the liver than in the spleen. It is this last approach which these authors favour but a further and perhaps rather less sophisticated argument may be adduced. This will be referred to later.

These arguments, though they may throw light on the differences in tumour distribution, still do not shed any light on the carcinogenic process itself and especially as to whether ionising radiation or a purely physical or even a physico-chemical mechanism is operating. Is there any evidence that a non-radioactive contrast medium whose uptake and tissue distribution is similar to Thorotrast can or cannot produce tumours?

Bensted and Crookall (1963) presented some evidence along these lines. These authors used a non-radioactive zirconium colloid, "Zirconotrast", which was distributed in mice in a fashion very similar to Thorotrast. It produced no apparent damage but there was very suggestive evidence of the so-called Thorotrast specific tumour, the haemangio-endothelioma, which indicates that this tumour need not be necessarily Thorotrast specific. On the other hand, Upton et al. (1956) after producing hepatomata in mice with radioactive colloidal gold then failed to produce any liver tumours with similar preparations whose radioactivity had been allowed to decay to negligible levels after 60 days. This would suggest that radioactivity is not entirely insignificant, but it should be pointed out that their tumours were all hepatomata and that the gold was complexed with gelatine to form the colloid (vide infra).

Whilst still maintaining a purely physical line of approach we could not unreasonably regard the production of Thorotrast tumours as an example, albeit a remote one, of the "Oppenheimer effect" i.e. the production of local tumours following the subcutaneous implantation of chemically unreactive materials such as polymer films (Oppenheimer et al., 1943 and 1952). Chemically, thorium is of low toxicity (Hodge et al., 1960), as witness the lack of evidence of radiation injury or of chemical toxicity in workers involved in the refining of thoria from monazite. Long term inhalation of thorium dioxide at levels of 9 mg Th/m^3 has produced no toxic effect in a variety of experimental animals. Polymer tumours are generally associated with a mass of granulomatous tissue or a fibrous capsule which is conspicuous by its absence in the case of experimentally induced liver tumours but is generally in the subcutaneous sarcomata. Oppenheimer was of the opinion that it was the fibrous capsule which was the site of origin of the neoplastic change, the incidence of the latter being related to the surface area of the films. Silva Horta et al. (1965) consider that the "Thorotrastomas" are prone to develop malignant tumours at their periphery, though Faber (1962) does not seem so convinced. Although the Thorotrast aggregates are small to start with, they increase in size with the passage of time (Guimaraes and Lamerton, 1956). On the other hand, Hueper (1959) does not consider that the carcinogenic effect of water-soluble polymers such as dextran (vide infra) is related to their surface area.

Thus, though the subcutaneous tumours may perhaps be regarded as an example of the "Oppenheimer effect", it is rather more difficult

to invoke this mechanism in the case of liver tumours, where at least in experimental animals there is remarkably little granulomatous reaction.

In the face of this conflicting evidence, we should perhaps turn to alternative explanations and it is tempting to study yet another mechanism which has some similar features, namely the carcinogenic properties of iron-dextran complexes. It is now well-established that subcutaneous injections of an iron-dextran complex, Imferon, result in fibro-sarcomas in rats and mice (Richmond, 1960; Haddow and Horning, 1960). Is there some relationship to Thorotrast here? Is the thorium-dextran complex acting in the same way as the iron-dextran complex, or is the dextran itself acting as a carcinogen?

Opinion as to the carcinogenic action of dextran alone is rather conflicting and this is not surprising since dextrans are of very varied molecular weight and shape. Hueper (1957 and 1959) investigated the carcinogenic properties of a great many polymers, particularly polyvinyl pyrrolidones (PVP) of molecular weight from 50,000 to 10^6, and 11 different dextrans with molecular weights from 37,000 to several million and with varied molecular shape (i.e. single or branched chains). The water soluble polymers such as dextran show their carcinogenic effect in sites where they are retained and stored such as the liver or spleen. With PVP compounds and the dextrans, Kupffer cell proliferations were noted in mouse livers and in rats, and Kupffer cell sarcomas were noted 19 - 21 months following injection. Here the comparison may not be strictly fair since the dextrans were given intravenously in multiple doses (10 - 20) whereas in the Thorotrast studies only one dose was given. Thus a dose comparison is difficult since for one thing there is little information on the molecular weights of the various dextrans used in Thorotrast or on their structure. This seems to be a factor since Hueper showed that carcinogenicity increased with increasing molecular weight. Neither Richmond (1960), Haddow and Horning (1959) or Lundin (1961), however, found tumours following dextran alone.

To turn again to the specificity or otherwise of the haemangioendotheliomas as "Thorotrast tumours", there is evidence that Thorotrast has distinct pharmacological effects especially on blood vessels. It is known from the work of Rowley (1963) that intravenous injection of Thorotrast will result in mast cell degranulation and increased vascular permeability. Rowley showed that it was the dextran component of Thorotrast which produced these effects in blood vessels and it is tempting to speculate that it is this vascular damage which may ultimately result in the formation of the vascular tumours.

In connection with the differential distribution of dextran in the tissues of the mouse, Turner and Maycock (1958) showed that for three weeks after the intravenous injection of dextran the liver contained several times more dextran per gram of tissue than the rest of the body. This observation may be related to the higher incidence of the vascular tumours in the liver.

Langvad recently described the production of haemangioendotheliomas of the liver (amongst other tumours, such as fibrosarcomata at the injection site) in mice given Imferon subcutaneously.

In view of the possibility of a viral infection from other strains it was suggested that the Imferon treatment had activated latent oncogenic viruses.

Thus, whilst several other mechanisms, none of which takes account of the radioactive properties of Thorotrast, have been reviewed as possible factors in the carcinogenic potential of Thorotrast, it must be admitted that the evidence for simple chemical or physical effects is still far from conclusive.

We still await results from experiments involving altered Thorotrast activity as suggested by Dudley (1962) in order to distinguish between the physical and chemical effects and the radiation effects of Thorotrast.

EPIDEMIOLOGICAL EXPERIENCE WITH THOROTRAST IN DENMARK

M. Faber

1. Introduction

In the Scandinavian countries Thorotrast has been used since 1932, first in Sweden and later in Denmark. Except for one case injected in a knee joint it has been used only in neurosurgical departments. This gives the advantage that we do not have to try to interpret cases injected on account of primary liver disease. The Swedish group has been partly described by Blomberg et al. (1963) and single cases have been published by Blomquist and Freidenfelt (1959), Larsson (1963), Dahlgren (1961 and 1962), Hassler et al. (1964), and Novik (1960). From Norway we have the interesting case of Halvorsen and Sander (1963). The Danish material has been presented by Faber (1962). The main content of this report will be a follow-up of the earlier one, with an increase in the number of cases described since we now know of close to 1000 injected patients. In the following I shall as far as possible present our material in relation to reports published from Sweden and those from Portugal (Silva Horta et al., 1965).

In Table 1 are shown the numbers of cases in the Danish group, classified according to amount of Thorotrast injected, sex, and status (living or dead) as of 1 January 1965. We know of a further 50 patients in whom the use of Thorotrast is doubtful; these are under observation, but are not included in this report. Table 2 shows the period of observation of both the living and dead cases. Table 3 compares the Danish, Portuguese, and Swedish cases with regard to age at time of Thorotrast injection. The 3 groups are very similar, with only a slight preponderance of younger persons in the Danish group. These age differences may be of significance for the slightly different incidence of cancer. The amount of Thorotrast injected into the Danish cases (Table 1) cannot be compared directly with the Swedish figures due to a difference in presentation of their data. Probably, however, injected amounts are similar in Denmark and Sweden, but lower in Portugal.

2. Non-malignant causes of death

The non-malignant causes of death of our cases, apart from neurosurgical diseases which I shall not describe in detail, are shown in Table 2. The two major disease groups involved are (1) the arteriosclerotic diseases of heart and central nervous system and (2) accidents and suicides (which sometimes may be difficult to differentiate in the epileptic patients).

Some of the diseases require further discussion. We have so far had only one case of death attributable to Thorotrastoma of the neck. Although we have reason to believe that the neck-injected patients represent about 10 per cent of the total (Backer et al., 1958) we have not met with malignant diseases in connection with these sclerotic lesions. The 3 cases of malignant tumours in connection with granulomas mentioned by Silva Horta et al. (1965) are interesting if they have occurred in connection with a sclerotic neck deposit as so far

TABLE 1

Danish Thorotrast cases

Thorotrast injected	Living			Dead									Total group		
				From neurosurgical diseases			From other non-malignant diseases			From malignant diseases					
ml	Males	Females	All	Males	Females	All	Males	Females	All	Males	Females	All	Males	Females	All
0-9	7	2	9	2	1	3	1	-	1	-	-	-	10	3	13
10-19	103	105	208	58	43	101	44	16	60	10[x]	1	11	215	165	380
20-29	89	73	162	60	43	103	28	19	47	5	7	12	182	142	324
30-39	21	25	46	16	10	26	8	6	14	3	2	5	48	43	91
40-49	10	14	24	10	6	16	6	4	10	2[x]	-	2	28	24	52
50	10	8	18	3	4	7	2	1	3	1	3	4	16	16	32
unknown	23	23	46	26	16	42	10	5	15	2	2	4	61	46	107
	263	250	513	175	123	298	99	51	150	23	15	38	560	439	999

[x] Hemangioendotheliomas

TABLE 2

Time of observation after injection of Thorotrast

Years	Males					Females				
	Dead from				Living	Dead from				Living
	Neuro-surgical diseases	Cancer	Other diseases	All dead		Neuro-surgical diseases	Cancer	Other diseases	All dead	
1	113		5	118		80			80	
2	14	1	5	20		10		2	12	
3	11		4	15		3	1	2	6	
4	5		3	8		6		1	7	
5	5	1	2	8		3	1	1	5	
6	2	1	6	9		2	1	2	5	
7			5	5			1	3	4	
8	2	1	4	7		5	1	4	10	
9	3		4	7		4	2	8	14	
10	5		4	9		1		2	3	
11	4	3	7	14		1		2	3	
12	4		11	15		1	1	1	3	
13		3	5	8		2		2	4	
14	1	1	6	8			1	4	5	
15	3	1	4	8	1	1	1		2	
16			2	2	2			2	2	1
17	1	1	4	6	6			5	5	7
18		1	3	4	18	2	1	1	4	18
19		1	4	5	12	1	1	4	6	3
20		1		1	22					13
21		2	4	6	28			1	1	28
22			1	1	23			1	1	28
23	1		2	3	27		2	1	3	23
24	1	2		3	49			1	1	30
25		1	1	2	38	1	1		2	43
26			1	1	35					50
27		1	2	3	2			1	1	6
28		1		1						
29										
30										
Total	175	23	99	297	263	123	15	51	189	250

TABLE 3

Age distribution of patients at time of injection

	Denmark	Portugal	Sweden
0 - 4	0.1	0.59	0.4
5 - 14	7.4	6.77	2.6
15 - 24	23.1	21.76	12.0
25 - 44	44.8	41.52	48.1
45 - 64	16.5	21.08	35.1
65 ⟶	0.1	4.29	2.7
unknown		4.00	

TABLE 4

Causes of death by non-malignant diseases apart from neurosurgical diseases

	F	M	Total
Arteriosclerotic heart diseases	13	25	38
Other heart diseases	2	3	5
Suicidium or veneficium	8	23	31
Accidents	2	8	10
Cerebral haemorrh.	10	15	25
Gastro intestinal diseases	3	6	9
Renal diseases	2	1	3
Infections	6	5	11
Neck deposit	1		1
Cirrhosis of the liver	3	1	4
Severe blood diseases (hemolytic)	1	4	5
Others	2	6	8
			150

Only a few sarcoma cases have been published (Novik, 1960; Dahlgren, 1961 and 1962; Plenge and Krückemeyer, 1954). In epithelial systems close to neck deposits it is possible that a carcinoma may appear. Fugazzola (1954) has described the occurrence of a larynx-carcinoma close to a neck deposit.

The next group to be discussed is that including the cases of liver cirrhosis and chronic hepatitis. We have in our group 4 cases of which 3 are females. From a clinical point of view the females have to be considered a late extention of the severe subchronic to chronic hepatitis which appeared during the last world war and had a mortality very close to 100 %. Our material therefore gives no support to the point of view that injection of Thorotrast into patients without a primary liver disease or other complicating liver problem will cause an increased incidence of fatal hepatic fibrosis.

The third group to be mentioned contains 5 cases of benign but fatal haematologic disorders, for whom details are given in Table 5. One of these, a case of myelofibrosis (No. 6) appeared at such an early time that we are inclined to believe it was present when the injection was given. There is one case of haemolytic anemia of unknown type, and 3 cases having clinically acute bone marrow failure with atrophy (some described as having Di Guglielmos' disease). Whether these can be attributed to Thorotrast is difficult to evaluate. The connection to Thorotrast is still weak but quite a number of cases have by now been described (from Scandinavia see Halvorsen and Sander, 1963, and Blomberg et al., 1963).

TABLE 5

Fatal non-malignant blood diseases

Case No.	Sex	Age at inj.	Thorotrast injected (ml)	Time from injection (years)	X-ray treatment	
3	F	24	15	24	+	Agranulocytosis
6	F	33	25	7	+	Myelosclerosis
23	F	27	30	23	-	Aplastic bone marrow
363	M	30	25	13	-	Haemolytic anemia
829	M	50	10	15	-	Di Guglielmos' syndrome

3. Malignant causes of death

The most important problem is of course whether there is an increase in cancer incidence among the patients injected with Thorotrast. This problem can be approached in two different ways. One is to compare the number of malignant tumors found in the injected group with what would be expected to be present if the group were part of the general population. On the basis of Clemmesen's valuable tables on cancer incidence in Denmark (Clemmesen, 1965) it is possible to calculate the expected

incidence of cancer in the Thorotrast group treating males and females separately. In this calculation the 1st of January of the year after the injection was used as the date of entrance and the year of death as the final year. The patients injected with Thorotrast are selected as being under observation for brain tumors. The expected incidence of this tumor has therefore been calculated and deducted from the total incidence of malignant tumors. On this basis we can calculate that the total group could be expected to give 39 cases dead of cancer (19.6 female, 19.4 male). The cancer cases actually observed (including one female still living 4 years after diagnosis of an ovarian carcinoma) are listed in Table 6. Surprisingly, the total number agrees with the prediction, although there is an excess of males (23) and a deficiency of females (16). If we compare the observed incidence in time with the calculated incidence we find that the 2 curves fit very nicely. Studying the Thorotrast group from this point of view it appears to be rather improbable that Thorotrast gives rise to an increased incidence of malignant disease.

If, however, we look at the details in Table 6, we see that the problem is not quite as simple as this. In the material we find 2 cases of hemangio-endothelioma, an incidence which is much higher than expected. Taking what is known of this tumor into consideration it is quite definite that these two cases would not be present if the group had not been injected with Thorotrast. The next problem arises when we note that the material contains 5 acute leukemias and 1 chronic myeloid leukemia. These cases could all be due to bone marrow irradiation but are still within the expected total incidence of cancer. Finally, we find 2 cases of pleural tumors. They are under re-evaluation since the Swedish material contains a case where a pleural tumor appeared to be a complication to a neck deposit (Novik, 1960). Taking these last mentioned 10 cases of malignancies into consideration it must be stated quite definitely that although the observed incidence of cancer is close to the expected incidence, there is reason to believe that Thorotrast can give rise to certain malignant tumors. It therefore appears that conclusions on the cancerogenicity of Thorotrast based on groups of the size of 1 to 3,000 cases, as has been seen the case so far, are completely inadequate to evaluate this problem. Not until a large series of cases (if possible 10-20,000) has been studied for about 25 years will it be possible correctly to evaluate to what extent the different groups of malignant tumors, apart from the hemangio-endotheliomas, are of significance.

If we leave the positive findings I think we can also mention an important negative finding in this Danish material. We have so far seen only one primary hepatic tumor, a frequency which is much less than that reported from Sweden or Portugal. On the other hand we have 2 intrahepatic bile duct carcinomas, which will bring the total number of liver tumors up to 3. For the whole group this is also more than calculated from the general population.

An important problem is of course whether the group of individuals under study has any innate risk of having malignancies of the types mentioned. I shall concentrate on the leukemias. In our last review of the malignancies of Thorotrast we concluded that the information we had on these patients was such that it was completely impossible to evaluate whether Thorotrast itself was significant or not. Out of the 4 cases of

TABLE 6

Cancer cases

Case No.	Sex	Location	Thorotrast injected (ml)	Duration of latency period to death (months)
		150-154 Digestive organs		
36	M	Stomach	18	291
41	F	Stomach	?	237
102	M	Stomach	9	286
122	M	Rectum	20	263
151	F	Colon	24	290
332	M	Small intestine	30	19
619	F	Rectum	10	103
756	M	Rectum	10	196
		155-156 Liver-Bile ducts		
25	M	Hemangioendothelioma	42	257
128	M	Hemangioendothelioma	15	321
157	F	Bile duct carcinoma	15	266
494	F	Liver, primary	20	226
749	M	Bile duct carcinoma	30	225
		160-164 Respiratory system		
10	M	Lung	15	158
61	M	Pleura	10	162
66	M	Lung	20	156
435	M	Lung	40	247
526	M	Pleura	10	156
951	M	Lung	?	121
1043	M	Lung, metastatic	?	123
		170 Breast		
147	F	Breast	52	157
1035	F	Breast	30	137
		171-176 Uterus and other fem. genital organs		
272	F	Ovary	10	79
655	F	Collum	10	55
807	F	Ovary	?	Living
927	F	Collum	20	176
		177-179 Male genital organs		
929	M	Prostate	10	59
		Other organs		
407	M	Thymus	20	63
		202-205 Lymph. and hematol. tiss.		
193	M	Ac. leuc.	24	258
242	M	Ac. leuc.	48	170
367	F	Ac. leuc.	50	205
502	M	Chron.myeloid leuc.	20	122
797	M	Ac. leuc.	30	234
976	F	Ac. leuc.	?	106
		Metastases		
110	F		30	67
135	M		15	87
565	F		20	30
844	M		10	211
1000	F		10	88

leukemia known at that time, 2 had had X-ray treatment on the skull, and 1 had been published as a case of leukemia after an antiepilectic drug. The 2 new cases which have appeared since then tend to indicate that Thorotrast increases the risk of leukemia. We furthermore have to add that one of the cases of bile duct carcinoma had bone marrow changes which have been described as being chronic myeloid leukemia. At the same time there was an aplastic bone marrow in the spinal column.

The amount of Thorotrast injected into these cancer patients is known in most cases. As seen from Table 7 there is no significant difference from that of the total injected population. If, however, we look at those cases where we suspect a specific cancerogenic effect of the Thorotrast, in the hemangiomas and the leukemias, we find a slightly different picture: half of these patients received more than 30 ml, a dosage given in only 17 per cent of the other cases.

TABLE 7

Distribution of amount of Thorotrast injected into patients

ml injected	0-9	10-19	20-29	30-39	40-49	50→	unknown
All patients							
Number	13	380	324	91	52	32	107
Percent	0.13	38.0	32.4	9.1	5.2	3.2	10.7
Cancer cases							
Number	1	14	9	5	3	2	4
Percent	0.3	36.8	23.7	13.2	7.9	0.5	10.5

4. Conclusion

I can conclude by referring to my final remarks of 1961 (Faber, 1962) with a very slight change. The study supports the point of view that intravenous Thorotrast is able to induce certain malignant tumors like the hemangio-endotheliomas, but that only further studies will tell us whether it can induce other tumors. The leukemias in the Danish material show how extended observation gives increasing support to the significance of Thorotrast in carcinogenesis in preference to a previous X-ray treatment, for which the latent period is becoming longer than generally accepted.

EPIDEMIOLOGICAL THOROTRAST EXPERIENCE IN PORTUGAL*

J. da Silva Horta, J.D. Abbatt,
and L.A.C.R. Cayolla da Motta

The main results of the Portuguese survey have already been published (Silva Horta et al., 1965). It must be emphasized that no special control group has been established for these patients and that the only yardstick for comparison of disease incidence is the very crude one available from national demographic data. Therefore the results can be quantitated only in a very crude way. Very limited physical dosimetry has been carried out on the Portuguese patients by Cohn, Gusmano, and Robertson of Brookhaven National Laboratory.

Our published paper presented results of the follow-up of the Thorotrast patients to the end of 1963, and we now have available data to June 1965. The results up to June 1965 are summarized in Tables 1 and 2. In Tables 3 to 6 further details are given on some of the 928 systemically injected traced cases.

It will be seen that the latent periods in the leukemia (Table 5) and other fatal blood dyscrasia cases are shorter than in, for example, the hemangioendothelioma cases. The mean latent period for the leukemias was 17 years (range 2 - 25 years), and for the other fatal blood diseases 19 years. (If the leukemia childhood case with 2-year latent period is excluded, the mean latent period for the whole group of fatal blood diseases is 18.5 years.) None of these cases had at any time received therapeutic irradiation. It is striking that seven of the eight leukemias were myeloid in cell type and only two of these were of the chronic type with an illness lasting more than one year. The remaining one was of an acute monocytic cell type. It should be noted that myelogenous leukemia, particularly running an acute course, is the type of leukemia now primarily associated with radiation induction - when there is evidence of radiation induction.

One of the most notable features of our investigations, so far, is this significant finding of an excessive number of leukemias and other fatal blood dyscrasias. It is difficult to avoid the conclusion that they are induced, at least in part, by radiation from the Thorotrast. One of the most puzzling features is the much longer leukemic latent periods observed here than in other radiation studies. Since in this instance continuous irradiation results from the internally deposited Thorotrast, the differing dosimetry is probably responsible. Dose rate may well play a part in this problem.

It is intended to follow our living patients to death, BUT this will only give a qualitative improvement in our data in view of the relatively small population available and the difficulties of establishing the true increase in incidence rates.

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Table 1

Numbers of Portuguese Thorotrast cases

Total	2380
Systemically injected	1869
Traced	1116
Traced and systemically injected	928
Systemically injected cases alive on 30/6/1965	223

Table 2

Summary of effects in 928 traced systemically injected cases

Effect	Number	Details
Granulomata	5	Table 3
Malignant tumor, edge of granulomata	4	
Liver tumor	25 total	Table 4
Hemangioendothelioma	(22)	
Hepatoma	(2)	
Cholangioma	(1)	
Leukemia	8 total	Table 5
Acute myeloid	(5)	
Chronic myeloid	(2)	
Acute monocytic	(1)	
Aplastic anemia	6	Table 6
Purpura	2	Table 6

Table 3

Details of granulomata cases

(Total of 85 cases, of whom 16 examined histologically)

	Cervical	Non-cervical
Number of cases	65	20
Death due to granuloma	10	2
Malignant neoplasms at edge of granuloma	2	2

Table 4

Details of cases with histologically examined liver tumors

Case No.	Sex	Purpose of administration	Quantity administered	Time admin/death	Histological diagnosis
1105	female	cerebral angiography	20 ml	3 years and 2 months	Necropsy - hemangioendothelioma of the liver
1093	male	arteriography of the limbs	74 ml	22 years and 3 months	- " -
268[a]	male	cerebral angiography	40 ml	25 years	Biopsy - hemangioendothelioma of the liver
724	male	hepatosplenography	60 ml	27 years	Necropsy - hemangioendothelioma of the liver, spleen and bone marrow
871[b]	female	cerebral angiography	20-30 ml	28 years	Necropsy - hemangioendothelioma of the liver
1098	male	cerebral angiography	36 ml	30 years	- " -
938	male	arteriography of the limbs	78 ml	30 years	- " -
729	male	cerebral angiography	20-30 ml	30 years	- " -
32	male	hepatosplenography	65 ml	30 years	- " -
94	male	hepatosplenography	60 ml	31 years	- " -
57	male	cerebral angiography	36 ml	31 years	- " -
51	male	cerebral angiography	20-30 ml	28 years	Necropsy - reticulum cell sarcoma of the liver, spleen and bone marrow
47	male	cerebral angiography	20 ml	24 years	Necropsy - hepatoma
871[b]	female	cerebral angiography	20-30 ml	28 years	Necropsy - hepatocholangioma on the edge of granuloma
22	female	cerebral angiography	20 ml	30 years	Necropsy - cholangioma of the whole liver with intense "fibrose"

a = Portuguese case published in Holland by R. Vellenga (1962)
b = This patient had two liver tumors.

Table 5

Details of leukemia cases

Case No.	Sex	Age at administration (year)	Purpose of administration	Volume of Thorotrast (ml)	Latent period (year)	Diagnosis
715	female	8	cerebral angiography	15	2	clinical and hematological - acute myeloid leukemia
1102	male	34	cerebral angiography	40	7	clinical, hematological and necropsy - acute myeloid leukemia
1082	female	50	limb arteriography	65	17	clinical and hematological - acute myeloid leukemia
272	male	45	limb arteriography	?	19	clinical and hematological - acute myeloid leukemia
556	male	54	cerebral angiography	20	19	clinical and hematological - acute monocytic leukemia, with an erythremic component
747	female	30	cerebral angiography	36	22	clinical and hematological - chronic myeloid leukemia (evolution of 2 years)
82	male	43	cerebral angiography	54	25	clinical and hematological - acute myeloid leukemia
797	male	39	cerebral angiography	36	25 or less	clinical, hematological and necropsy - chronic myeloid leukemia

Table 6

Details of cases with aplastic anemias (pancytopenias) and purpuras

Case No.	Sex	Age at administration (year)	Purpose of administration	Volume of Thorotrast (ml)	Latent Period (year)	Diagnosis
261	female	48	cerebral angiography	20	12	Aplastic anemia with clinical, hematological and necropsy diagnosis
33	female	24	aortography	40	8	- " -
1096	male	35	hepatosplenography	60	21	- " -
41	male	18	cerebral angiography	36	21	Aplastic anemia with clinical, and hematological diagnosis
872	male	12	cerebral angiography	20 - 30	25	- " -
956	female	29	limb arteriography	40	25	Aplastic anemia with clinical diagnosis
25	male	16	cerebral angiography	36	24	Purpura with clinical, hematological and necropsy diagnosis. Died 24 years after with the diagnosis of purpura
710	male	31	cerebral angiography	16	?	Purpura with clinical diagnosis. Died 25 years after with the diagnosis of purpura
1098	male	29	cerebral angiography	36	29	Purpura with clinical, hematological and necropsy diagnosis. Died 29 years after with liver hemangioendothelioma
94	male	21	hepatosplenography	60	?	Purpura with clinical diagnosis. Died 31 years after with liver hemangioendothelioma
31	female	26	cerebral angiography	18	20	Purpura with clinical and hematological diagnosis. Alive
135	female	30	cerebral angiography	18	30	- " -

EPIDEMIOLOGICAL STUDY OF THOROTRAST INDUCED MALIGNANCIES IN JAPAN

K. Tsukamoto

A Japanese research group (Table 1) on radiation carcinogenesis in man was established in 1961. One project which it has undertaken is the investigation of the induction of cancer by Thorotrast. The general study consists of 3 largely independent surveys: a prospective and a retrospective epidemiological survey, and a statistical analysis of autopsies in which Thorotrast was reported. The results of the various investigators will be published in Acta Radiologica Japonica. Data from some of them (especially those of Prof. Takahashi) are included in my present report.

1. Prospective study*

This investigation was conducted chiefly by Mori and co-workers of Yokohama University School of Medicine. They examined about 20,000 clinical records of wounded soldiers in 4 large army hospitals near Tokyo and Yokoham . From these records they were able to identify 147 patients on whom angiography with the aid of Thorotrast was conducted. All were males injured in battle during the period 1935 - 1943, and they were injected with 3 - 75 ml Thorotrast at age 20 - 36. Great efforts were made to follow up these 147 cases, with the following results as of 1964: 112 cases (76.2 %) were still alive and healthy, 27 (18.4 %) were already dead, and 8 (5.4 %) were lost. Among the 27 deaths there are 3 cases of primary liver cancer histologically confirmed as cholangiocarcinoma, 2 cases of cirrhosis of liver, 1 case of leukemia, 10 cases of inflammatory diseases, 5 cases of other non-malignant diseases, and 6 cases of unknown causes.

These results were compared with the frequencies and causes of death in a control group of 1978 wounded soldiers who were from the same 4 army hospitals but had not been examined with Thorotrast. Of these, 1209 (72 %) were alive and healthy, 217 (13 %) were dead before 1963, and 252 (15 %) were lost. Among the 217 deaths there were 1 cases of leukemia, 5 of liver cirrhosis, 8 of stomach cancer, 1 of rectal cancer, 1 of osteosarcoma, 2 of brain tumor, 170 of other non-malignant diseases, and 29 of unknown causes. There are several statistical models which can be used in comparing these controls with the Thorotrast cases. It appears that all malignant diseases, including leukemia, which were observed in the Thorotrast cases had a greater frequency in this group than in the controls, but that only the elevation of liver cancer (cholangiocarcinoma) is significant at the 1 % level.

Finally, the cancer incidence rates in the Thorotrast cases were compared with those in the general Japanese male population over 30 years of age in 1951. The calculations indicate that the incidence of leukemia and liver cancer is significantly higher in the Thorotrast cases than in the general population.

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* **Ed. note:** The detailed results of this study were subsequently published in English by Mori et al., 1967, and only a brief summary is included here.

Table 1

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Tadashi Adachi	Dept. of Radiol., Tokyo Medical and Dental Univ.
Tadashi Hashizume	Div. of Physics, National Institute of Radiological Sciences
Yoshio Hashimoto	Dept. of Surgery, Nagoya Univ., School of Med.
Shiro Sakuragi	Dept. of Radiol., Tokyo 2nd National Hospital

2. Retrospective survey

In this study by Kitabatake and colleagues at the University of Nagoya School of Medicine, the frequency of occurrence of Thorotrast in patients with liver cancer was compared with its frequency of occurrence in patients without liver cancer. Questionnaires were sent to 970 departments of internal medicine and surgery in large hospitals in Japan having over 250 beds. They were requested to give (1) the number of patients with reticulant diseases of all types, (2) the name, sex, age, histological diagnosis, and X-ray findings in the abdomen of the patients with primary liver cancer diagnosed clinically from 1 Aug. 1962 to 31 July 1963. 202 departments (20.8 %) responded to this survey with 19,517 patients. 518 cases (2.6 %) were clinically diagnosed primary liver cancer, and of these, 234 (52.2 %) were histologically confirmed. Since in our country most of the Thorotrast injections were before 1935, and in patients over 10 years of age, all cases from among the 518 at present under 40 years of age were excluded from the statistical evaluation. From the residual number of 466 patients (Table 2) there were 140 hepatoma cases, 61 cholangiocarcinomas, 1 sarcoma of uncertain character, and 264 cases not examined histologically. Four cases of cholangiocarcinoma (0.85 %) with Thorotrast shadows in the hepatic and splenic regions on the abdominal X-ray film were all histologically confirmed.

Table 2

Age distribution of liver cancer patients (age 40 years) in retrospective survey

Sex	Age 40 - 49	50 - 59	60 - 69	70 - 79	≥80	Total
Male	51	130(3)	109	32	2	324(3)
Female	17(1)	50	58	16	1	142(1)
Total	68(1)	180(3)	167	48	3	466(4)

To construct a control population for these cases, 8500 employees (or members of their families) were selected from several kinds of companies in Aichi prefecture. All were over 40 years of age and none were receiving any kind of medical treatment at the time of examination. Four abdominal radiographs (6 x 6 cm) were made on each person: erect PA, erect oblique, prone, and supine projections. Before these films were read, however, a random selection was made among the cases so as to give exactly 3 times as many subjects in each age group as there are liver cancer cases (Table 2). These subjects were considered to be the control population. (This selection was required since among the 8500 employees or family members there were not enough individuals over 80 years of age to allow a larger control group.) Of 1398 controls thus chosen, Thorotrast shadows in the liver-spleen region were detected in only 1 case (0.07 %).

Statistical analysis showed the frequency of occurrence of Thorotrast in the liver cancer cases to be greater (significant at the 5 % level) than in the controls.

This retrospective survey is inferior to the prospective survey previously described in that it does not reveal the absolute risk of liver cancer from Thorotrast. However, since in the retrospective survey there are no cases of unknown prognosis, it is superior to the prospective survey in showing a positive association between the administration of Thorotrast and the development of liver cancer.

3. Analysis of autopsy data on Thorotrast cases

Pathologists of large hospitals in Japan were requested to report autopsy data on patients containing Thorotrast to Prof. Miyakawa, Dept. of Pathology, Nagoya University School of Medicine. Of 228 questionnaires sent to the pathologists, 124 (54.4 %) were returned. Thirty-eight Thorotrast cases were reported from 20 hospitals. Of these 38 cases, 21 were primary liver malignancies and one was a metastatic liver cancer.

A comparison was made of the frequencies of occurrence of various types of primary liver malignancies in the Thorotrast cases and the frequencies in 100 primary liver malignancies recorded in the "Japanese Autopsy Report 1962". As shown in Table 3, the proportion of cholangiocarcinoma and endothelioma was much higher in Thorotrast patients than in general autopsy cases without Thorotrast, while the proportion of hepatomas was lower. Statistical analysis shows these differences to be highly significant.

A comparison was made between the latent period (interval between Thorotrast injection and onset of disease) and the known or inferred amounts of Thorotrast injected in 9 cases of cholangiocarcinoma. The average latent period for 3 persons who received probably 60 - 75 ml (hepatolienography) was 20.3 years, and for 6 subjects who received less than 30 ml (angiography) it was 25.0 years. It therefore appears likely that the latent period is shorter for larger amounts of injected Thorotrast.

Table 3

Relative proportions of various primary liver malignancies in autopsy case study

Disease	Percentage of cases in general autopsies	Thorotrast cases	
		Number expected	Number observed
Hepatoma	68 %	18	5
Cholangiocarcinoma	28	8	17
Endothelioma	2	1	5
Others	2	0	0
Total	100 %	27	27

4. Discussion

The best way to study the late effects of radiation in man is the epidemiological method, since experiments are impossible. Because of the long latent period and low incidence for late effects, prospective studies are believed to be the most reliable. Furthermore, they are in principle capable of yielding information on absolute risk and on the dose-effect relationship. Therefore we conducted a prospective survey first.

While Thorotrast was in earlier years widely used in Japan for angiography and hepatolienography (see, for example, Okinaka et al., 1957), follow-up has been difficult because so many clinical records were burned in air raids during the Second World War. In the 4 hospitals whose records remained available for this study, the patients were not representative of the general Japanese population since they were all males (wounded soldiers) aged 20 - 39. On the other hand this sample had an advantage because the relatively low age of the patients has permitted follow-up for a comparatively long period.

In this prospective survey we could not give precise statistical conclusions because too many deaths were from unknown causes. This complication arose not through lack of effort, but through difficulties in tracing cases in the aftermath of the war. Furthermore, we have been unable to discuss a dose-effect relationship because of the small number of cases (only 3 with liver cancer) and the difficulties of assessing dose to the liver.

As a result of these inadequacies in the prospective study we also undertook the retrospective study. Although it is incapable of yielding an estimate of risk, it does permit a statistical evaluation uninfluenced by unknown causes of death.

Our reason for making these studies, despite the insufficient numbers of cases, was that it will be difficult in Japan to obtain larger groups for either prospective or retrospective surveys.

Despite these difficulties, the research groups believe the conclusion can be drawn that the incidence of primary liver malignancy, particularly cholangiocarcinoma, is higher in Thorotrast cases than in the normal population.

THOUGHTS ON FUTURE STUDIES OF THOROTRAST CASES

J. D. Abbatt

It is important to use the opportunity provided by the availability of the world's internally irradiated Thorotrast population because it is an opportunity for gaining knowledge that will not recur. Moreover, this opportunity will disappear if an international cooperative study is not started very quickly. We know that Thorotrast patients have been listed and to a varying extent investigated in at least: Austria, Canada, Czechoslovakia, Denmark, Japan, Portugal, Sweden, U.K., U.S.A., West Germany.

The qualitative nature of the effects is now known: manifestations at the site of injection such as granulomata and tumors, liver tumors including hemangioendotheliomata, leukemia and some assorted blood dyscrasias, and possibly lung cancer.

Physical dosimetry is fairly good but is useless without effect data.

Quantitative biological information is not available, nor, with present populations and methods at present foreseeable, are the precise yields of different effects from given radiation dosages.

This quantitative information can probably only be obtained from a planned cooperative study of a "series of series", and only if this irradiatied human material is handled in the most efficient way possible. Speed is essential since the world's Thorotrast population is rapidly disappearing through death.

In the light of our own experience we would like to second appeals that have been made for more effort, and to suggest that a cooperative study should be set up to follow at least all those living Thorotrast patients now known to exist, the follow-up to continue to the extinction of this population.

If any such attempt is made, and if the different effects of Thorotrast are shown to be statistically significant and are quantitated at different dose levels, they will have different potential uses and values for extrapolation to other internal emitters.

Any local tumors resulting from Thorotrast, and the dose-effect incidence of such tumors, could probably only be properly applied to Thorotrast. This information, though useful, will be of limited value. The same is true of liver tumors and tumors involving the reticuloendothelial system, though possibly to a slightly lesser degree. It may even be true of leukemia, though the long latent periods after Thorotrast administration are intriguing to say the least, and justify

the study of these cases. On the other hand, if there should be an increased incidence of either lung and/or bone tumors, dose-effect knowledge of this increased incidence could be of considerable value since dosimetry is likely to be reasonably good. Negative information on these two latter points might be of value equal to positive information.

For the reasons outlined above, it would seem profitable to give more thought to a possible increased incidence of leukemia, lung and bone tumors than to the other possible effects, and to pay particular attention to constructing a control population(s) which might allow firm conclusions on the incidence of these effects to be drawn at the end of the investigation. This would seem a reasonable and necessary approach since most of the patients injected with Thorotrast have had miscellaneous but serious disease processes present at the time of administration. This makes the provision of a good control group difficult, but there is no known evidence to suggest that Thorotrast cases, by virtue of the disease processes leading to Thorotrast administration, are either more or less likely than any other section of the population to develop leukemia, or lung or bone tumor.

Bearing in mind the general comments above, three suggestions are made for a control population. It is almost certain that no perfect control population can be obtained. The best that can be done would probably be to operate with multiple control populations each of which should control different possible variables.

(1) National Death Registration data. Not too much reliance can be placed on any comparison with national death registration data alone even if such a comparison is possible. There are a number of objections to the validity of any such comparison, the most important being that the Thorotrast patients represent a selected diseased group at the time of Thorotrast injection. In addition, with very few exceptions, it is not possible to compare different national death registration data directly, since widely different systems are still in use in different countries.

(2) Patients injected for conditions similar to the Thorotrast cases, but with non-radioactive contrast media, during the period before, during, and after Thorotrast was used, may provide a reasonably good control group in some respects. This will provide a reasonable control group matched moderately for pre-existing disease (i.e., also selected).

(3) Another control population not matched for disease, but matched for familial and environmental effects, would be composed of the brothers of male patients (failing a brother, a male cousin) and the sisters of female patients (failing a sister, a female cousin).

An objection to both these latter groups is the limited extent to which retrospective information can be obtained. It will frequently not be possible to obtain information on certain possibly important

factors such as smoking habits. This will, of course, apply equally to both the Thorotrast and control populations though the equal application of this objection to both groups does not make the objection any less valid!

The remarks I have made are not meant to suggest the definitive outline for an investigation, but the suggestions may provide a basis for discussion in developing such a definitive outline.

There are three main aspects of the epidemiological problem that, at the risk of repetition, I would like to repeat:

(1) No single series alone will yield the information that we need.

(2) The information needed is particularly that on leukemia, lung and bone tumor incidence, and the associated radiation dosimetry. Positive or negative information will probably be of equal value.

(3) Speed is essential. Speed of decision and of implementation is essential if a cooperative study is to succeed.

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