POST-IRRADIATION CHANGES AND DOSE DETERMINATIONS IN THORIUM-IMPREGNATED LIVER AND SPLEEN A CASE REPORT

Noritoshi Watanabe, M.D.[1*]
Tatsuo Mandai, B.S.[2**]
Walter J. Russell, M.D.[1***]
Haruma Yoshinaga, Ph.D.[3****]

Department of Radiology[1] and Radioisotope Laboratory[2], Atomic Bomb Casualty Commission and Research Institute for Nuclear Medicine and Biology[3], Hiroshima University, Hiroshima, Japan

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肝臓および脾臓のトリウム沈着による照射後変化および線量測定

（症例1）

渡辺哲敏　万代達男
Walter J. Russell　吉永春馬

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二酸化トリウム使用の歴史を簡単に総括した．組織内におけるトリウム沈着値の推定および線量計算に当つて遭遇した若干の困難について述べるとともに，22年前のトロトラスト静注患者の組織を用いて実施した化学検査，X線写眞およびオートラジオグラフィによる研究成果を合わせ紹介した．この患者においては肝臓および脾臓の推定被照射線量はそれぞれ 680 rem および 25000 rem であつた．

Present address: *Radiology Department, Faculty, of Medicine, Tokyo University, Tokyo, Japan
**Radioisotope Laboratory, Atomic Bomb Casualty Commission, Hiroshima, Japan
***Chief, Radiology Department, Atomic Bomb Casualty Commission, Hiroshima, Japan
****Professor, Department of Experimental Radiology, Faculty of Medicine, Kyushu University, Fukuoka, Japan

BACKGROUND

The early use of thorium and other radioisotope materials in medicine and industry has been reviewed by Looney[1]. Thorium was first applied clinically in 1928[2,3] to visualize the liver and spleen radiographically and gradually became more widely used for this purpose[4,5] and as a contrast medium for bronchography, carotid angiography and cerebral angiography.[1] It was also used to visualize genitourinary structures,[6] in placentography, mammography and in angiography of the extremities.[1] Its usefulness in detecting accessory spleens was also reported.[7] Due to its ability to concentrate mainly in the histiocytic elements of the liver and spleen, its greatest value continued to be in hepatolienography.

Earlier analyses of cases in which thorium was administered failed to produce convincing evidence of early or late damage attributable to it.[8,9] Immediate or early histological changes attributed to thorotrast were reported in laboratory studies by Wen[10] and Pohle[11] in 1933 and 1934. Thorotrast is a colloidal suspension containing 20 per cent thorium dioxide and 20 per cent dextron with 0.15 per cent methyl-p-hydrobenzoate as a preservative.[12]

Thorium is radioactive with a half life of 1.4×10^{10} years. Most of its effect is caused by alpha radiation (90 per cent), with a small contribution by beta (10 per cent) and gamma rays (1 per cent).[13] Early investigations showed that the majority of the material intravenously administered to laboratory animals and patients was immediately deposited in the liver and spleen and that only very small amounts were excreted.[14] Because of its radioactivity and its prolonged retention, early warnings of possible late effects were issued[14,15,16] and in 1932 the Council on Pharmacy and Chemistry of the American Medical Association refused to endorse it for intravenous use.[12] Some who used it clinically suggested it be restricted to patients in older age groups, with serious disease, and with a short life expectancy.[11,17,5] In 1947, MacMahon[18] reported the first neoplasm in a patient attributable to the use of thorotrast, and subsequently an additional number of neoplasms of wide variety have been documented. They were summarized by Baserga[19]. (Figure 1)

Neoplasms were produced in laboratory animals[20] by thorotrast injections in 1949. Additional neoplasms of the renal pelvis,[21] liver[19] and other sites have been reported. Amory[22] and others have pointed out that severe and often incapacitating fibrotic changes occur at the sites of intravenous administration of thorotrast, particularly if there is extravasation. It has been emphasized that the fibrotic changes which result from its administration are due to the radiation, rather than a nonspecific reaction.[23] Cases of aplastic anemia have also been attributed to thorotrast administration.[24,25] Dahlgren[13] and others have pointed out the importance of documenting all cases of thorotrast administration, and that all such cases should be given periodic follow-up examinations in an attempt to detect more cases of neoplasia.

Immediately following the injection of thorotrast the deposit of the compound has been reported to be 50 per cent[15] and 60 per cent[26] in the liver and 10 per cent[15,26] in the spleen. Deposit in the liver 5 years after injection was reported 27 per cent by Jacobson and Rosenbaum.[27] Okinaka[28] reported a deposit of 18.7 per cent in the liver and 25.8 per cent

Figure 1 Malignant Tumors in Man Attributed to Injection of Thorotrast[10]

Type tumor	P. age, yr.	Pt. sex	Latent period, yr.	Amount & route injection	Reference
Endothelial cell sarc. liver	70	F	12	75 ml. intravenous	MacMahon et al.
Spindle cell sarc. kidney	64	M	16	30 ml. retrograde pyelography	Zollinger
Carc. breast	47	M	12	? intraductal	Austoni
Carc. eyelid	51	M	35	? in lacrimal duct	Rudolphi
Squam. cell carc. maxillary sinus	64	F	10	? into maxillary sinus	Hofer
Bronchogenic carc.	47	M	18	? bronchography	Vogtlin & Minder
Endothelial cell sarc. liver	···	F	3	20 ml. intra-arterial	Horta
Hemangioendothelioma liver	63	F	14	24 ml. intra-arterial	Ludin
Carc. extrahepatic biliary ducts	39	M	22	? intravenous	Heitmann
Carc. liver	53	F	21	80 ml. intravenous	Matthes
Sarc. at site injection	54	F	6	20 ml. arteriography	Plenge & Kruckemeyer
Carc. maxillary sinus	36	M	15	? into maxillary sinus	Gros et al.
Hemangioendothelioma liver	49	M	12	? intra-arterial	Fruhling et al.
Malig. peritoneal "thorotrastoma"	60	F	17	24 ml. intraperitoneal	Scheibe
Hemangioendothelioma liver	54	M	14	? intra-arterial	Tesluk & Nordin
Carc. kidney	75	M	?	? ?	Boemke
Cholangiocarc. liver	54	M	21	? intra-arterial	Grossiord et al.
Bronchogenic carc.	75	M	16	? ?	Hackenthal
Angioblastic sarc. liver	46	M	22	? intra-arterial	Horta
Cholangiocarc. liver	52	F	21	70 ml. intravenous	Matthes
Carc. extrahepatic biliary ducts	45	F	17	? intra-arterial	Roberts & Carlson
Carc. liver	58	M	12	? intra-arterial	Batzenschlager & Wilhelm
Carc. breast	43	F	17	? intraductal	Brody & Cullen
Carc. liver	37	M	13	? intra-arterial	Federlin & Scior
Carc. ovary	45	F	23	? salpingography	Schwenzer & Federlin
Bronchogenic carc.	38	M	13	? bronchography	Roth
Carc. pancreas& kidney	70	M	13	? intra-arterial	Wuketich & Mark
Endothelial cell sarc. liver	61	M	24	75 ml. intravenous	Grampa & Tommasi-niDegna
Carc. liver	48	F	24	? intravenous	Morgan et al.
Adenocarc. lung	43	M	24	? intravenous	Nielsen& Kracht
Mixed tumor kidney	66	F	?	? ?	Nielsen & Kracht
Carc. seminal vesicle	68	M	14	? urethrovesicography	Gelzer & Scheidegger
Carc. liver & lung	57	M	19	? intra-arterial	Werthemann
Hemangionsarc. liver	50	M	13	80 ml. intra-arterial	Rosenbaum
Giant follic. lymphoma spleen	65	F	15	15 ml. intra-arterial	Gardner & Ogilvie
Carc. left hepatic duct	47	F	24	? intra-arterial	Gardner &Ogilvie

in the spleen 11 years after injection. Shimanouchi[29] reported 11.3 per cent deposit in the liver and 1.35 per cent in the spleen 17 years after injection.

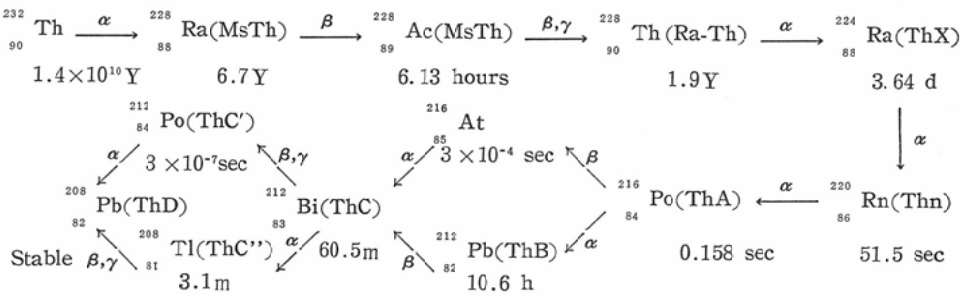
In calculating dose to the tissues, the distribution of the thorium, the distribution and excretion of thorium daughters formed in the body, the excretion of thorium as a function of time following injection and the self-absorption of particle energy within the deposits of thorium must be considered.[30] A large number of small deposits of thorium in an organ may be expected to give a relatively uniform dose to the organ; larger aggregates may contribute a nonuniform dose, and there may be self-absorption within them.[30] Therefore doses vary widely within an organ and among organs of different cases.[30]

Quantitative autoradiography, radiochemical and spectrochemical procedures should be employed in dose determinations where possible. Hursh et al.[31] calculated that an individual who received 15 gm. of thorium in 75 ml. of thorium dioxide received the following doses per week: Liver, 1.5 rad; spleen, 2.5 rad; bone marrow, 0.3 rad. Rotblat and Ward[30] presented the following doses per week of a patient who received 22 ml. of thorium dioxide intravenously: Spleen, interior 4.8 rep; spleen, exterior 8.3 rep; spleen, hilum, 3.5 rep; and liver, 8.1 rep. Rundo[32] calculated cumulative dose in rep to the liver, spleen and bone marrow for a standard man following the injection of 20 ml. of thorotrast, as shown in Figure 2. Figure 3 illustrates the decay of thorium.

Figure 2 Cumulative Dose (Rep) to Liver, Spleen, and Bone Marrow for a Standard Man After Intravenous Adminstration of 20 ml. Thorotrast[32]

Organ	Weight	Th. content		After 5 years Alpha	After 5 years Beta	After 10 years Alpha	After 10 years Beta	After 20 years Alpha	After 20 years Beta
Liver	1700	70%	2.8gm.	109 61	7.3 2.7	316 189	16 11	726 695	42 36
Spleen	150	25%	1 gm.	310 117	25 9	580 354	56 38	1320 1100	149 130
Bone marrow	1500	5%	0.2gm.	6.3 2.4	0.5 0.2	12 7	1.1 0.6	27 22	3.0 2.6

Figure 3 Decay of Thorium



CASE REPORT

A 46 year old Japanese male received thorotrast intravenously for purposes of visualizing the liver, 22 years previously. Clinical information concerning the patient's earlier history and physical findings was lost during the confusion of World War II. It is not possible to reconstruct the patient's history accurately, but it is known that he had a

cholecystomy in 1938, in Manchuria. The administration of thorotrast presumably took place just before this surgery. The amount administered is not known.

On January 5, 1960, a Hiroshima hospital diagnosed the patient as having liver disease on the basis of physical findings, but he refused hospitalization. Clinically, a neoplasm secondary to thorotrast administration was suspected.[33] He developed jaundice and malaise 2 days later. When finally hospitalized 4 months later he was found to be anemic (RBC 2,090,000/mm^3; Hgb 8.5 gm per cent) and had a moderate leukocytosis (WBC 14,200) and ascites. Liver function studies were abnormal; icterus index was 120; van den Bergh: direct, 4+; indirect, 4+. Paracentesis was performed and 800 cc. whole blood transfused during that admission. He expired June 29, 1960.

An autopsy (#60-AH-118) was performed at the Atomic Bomb Casualty Commission (ABCC), Department of Pathology. Gross findings included absence of the gallbladder, stenosis of the orifice of the common bile duct, dilatation of hepatic ducts, moderate biliary cirrhosis, 3,500 cc. ascitic fluid and esophageal varices with hemorrhage. Histological findings included chronic passive congestion of the spleen, with hemorrhage, fibrosis, hemosiderosis and extensive thorium deposits in the stroma of axillary and inguinal lymph nodes. Sections of the stomach and ileum showed chronic inflammatory changes. The liver showed extensive secondary biliary cirrhosis, proliferation of bile ducts, regeneration of liver, and deposition of thorium mainly in Kupffer cells. Bone marrow of the sternum and rib cage showed deposition of thorium and fibrotic changes. There was moderate cholemic nephrosis involving both kidneys. The formalin-fixed tissues were analyzed 6 months after death.

ANALYSIS OF TISSUE

Radiography

Sections of the formalin-fixed liver and spleen 1.5 cm. in thickness each were used to make the roentgenograms shown in Figure 4. These roentgenograms were made using 58 kilovolts, 5 milliampere seconds, and employing the usual processing techniques.

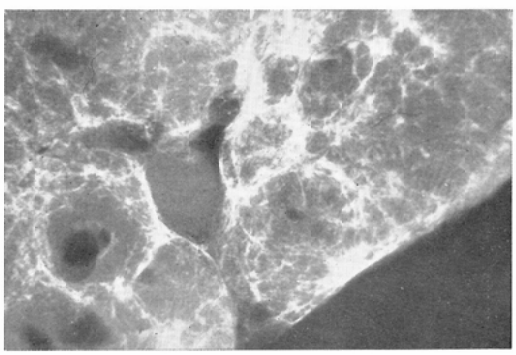


Figure 4(a)

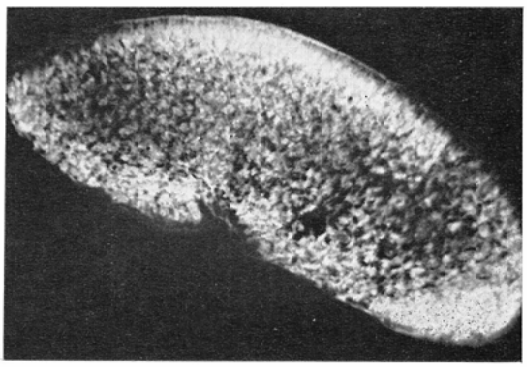


Figure 4(b)

Radiographs of sections of (a) liver and (b) spleen, showing aggregates of thorotrast in tissue, and fibrotic change secondary to the thorotrast. (Five times)

There is a relative increase in the amount of dense tissue in the affected liver and spleen, representing fibrosis. The histological findings at autopsy confirmed the presence of such fibrotic change.

Autoradiography

Sections of the liver and spleen 5μ in thickness were used for autoradiographic analysis, employing a Kodak-nuclear 5μ emulsion, using the stripping method. Numerous alpha tracks were visualized on the emulsion, and are shown in Figure 5. Fibrotic changes in the connective tissue are also visible. Also seen are large numbers of small aggregates of approximately 5μ in diameter each and a very small number of large aggregates of thorotrast.

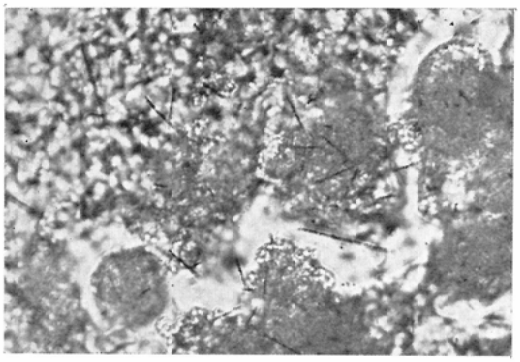


Figure 5 (a)

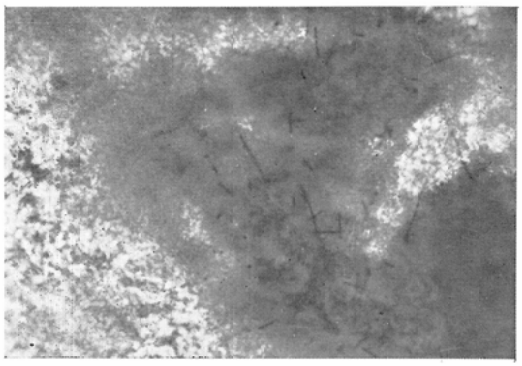


Figure 5 (b)

Autoradiographs of the (a) liver and (b) spleen showing numerous alpha tracks in tissue.

Chemical Analysis and Dosimetry

The method used was that described by Ishibashi and Azuma[34] in which ashed samples of the organs were acidified and dissolved and the thorium was precipitated by centrifugation. The precipitate was analyzed by colorimetric method. In our study, the wet liver specimen weighed 1,670 gm. and the wet spleen specimen weighed 55 gm.

By chemical analysis calculations showed a deposition of 0.37 mg. of thorium per gram of liver and 13.7 mg. of thorium per gram of spleen. The total thorium in the liver was 0.62 gm., while that in the spleen was 0.75 gm. The amount of thorium in the liver was calculated to be 0.068 μc, while that in the spleen was 0.082 μc, according to the following formula.

Formula:

$$C = (K)\frac{(W)}{(A) \cdot (T)}$$

C = activity in curies

W = radioisotope weight in grams

$$K = \text{constant} = \frac{6.02\times10^{23}}{3.7\times10^{10}\times1.44}$$

A = mass number

T = half-life in seconds

By knowing the effective absorptive energy for the organ of reference, in terms of thorium and its daughters (Fig. 3), the dose to each organ was calculated according to the following formula:

$$R\,(\text{rem}) = \frac{(\text{disintegrations/sec/}\mu\text{c})(\text{effective energy})(\mu\text{c thorium per organ})(\text{time in sec})\frac{(\text{erg/MEV})}{100}}{\text{organ weight in grams}}$$

According to International Committee for Radiation Protection (ICRP),[35] effective energy is expressed as Σ EF (RBE)n. Here it is assumed to be the same for liver and spleen, and the values for these organs is expressed as 41, according to ICRP.

The time, 22 years, expressed as seconds is 6.9×10^8.

Making appropriate substitutions in the formula, the dose for the case in this report was calculated as follows:

(a) Liver

$$R\,(\text{rem}) = (3.7\times10^4) \times 41 \times \frac{0.068}{1670} \times 6.9\times10^8 \times \frac{1.6\times10^{-6}}{100} = 68\times10^1$$

$$R\,(\text{rem}) = 680$$

(b) Spleen

$$R\,(\text{rem}) = (3.7\times10^4) \times 41 \times \frac{0.082}{55} \times 6.9\times10^8 \times \frac{1.6\times10^{-6}}{100} = 25\times10^3$$

$$R\,(\text{rem}) = 25{,}000$$

Dose to the liver was 680 rem; that to the spleen was 25,000 rem.

Scintillation Counter Study

Using a thorium standard of 8.41 gm., wet samples of liver (0.45 gm.) and spleen (0.42 gm.) were counted in a well scintillation counter. It will be noted from Table I that the total volumes of thorium in the liver and spleen were estimated to be 0.58 and 0.76 gm. respectively by use of the scintillation counter. The results obtained by chemical analysis and scintillation counting are shown in Table I.

Table I

Sample	Weight (gm.)	Scintillation Counting Method			Chemical Method	
		C/M	Net C/M	Total Thorium per organ (gm)	Total Thorium per organ(gm)	Total Thorium in μc
Patient's Liver	1670	236	35	0.58	0.62	0.068
Patient's Spleen	55	1498	1297	0.76	0.75	0.082
Normal Liver	—	201	—	—	—	—
Normal Spleen	—	197	—	—	—	—
Th-St 8.41mg.	—	2107	1892	—	—	—
Background	—	202.4	—	—	—	—

In this counting procedure, it is difficult to estimate the radioactivity of daughters in organs which have been removed; therefore, the values of scintillation counting were used only as a supplemental reference.

DISCUSSION

Calculation of dose to organs and tissues in which thorium dioxide has been deposited

is extremely difficult. A small amount of the thorium and its daughters are excreted from the body; self absorption of alpha particles occurs in the aggregates of thorium in the tissues; and there are difficulties in studying thorium distribution in tissues. Dose estimates have a wide variation, and the factor may be as low as 2 or as high as 20 within an organ.

In spite of the difficulties encountered in determining the amount of thorium dioxide in the tissue, and in the calculation of dose to the tissue impregnated, a reasonable estimate can be made by chemical analysis of the tissue, by quantitative autoradiographic examination and making appropriate calculations. Even though there is a likelihood of significant error in these methods, it is still very useful to make these determinations.

SUMMARY

A brief review of the history of the use of thorium dioxide is presented. Some of the difficulties encountered in estimating amounts of thorium in impregnated tissue, and making dose calculations are cited. Results of chemical analysis, radiographic and autoradiographic studies of tissues of a patient who received intravenous injection of thorotrast 22 years previously are also presented. Estimates of dose to the liver and spleen of this individual were, 680 rem and 25, 000 rem respectively.

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