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# Thorium Dioxide Angiography Followed by Bile Duct Carcinoma; A Case Report with Radiological Studies

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二酸化トリウム注入による血管造影術に続発した胆管癌  
放射線学的検査を行った症例についての報告

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要約 23年前に二酸化トリウム剤注入による血管造影術を受けた47才の日本人男性の胆管癌による死亡例について報告した。各種剖検材料のX線検査、オートラジオグラフィ、スペクトル分析、化学的検査およびシンチレーション測定の結果、

肝臓、脾臓および頸部組織内に造影剤の存在を確認し、本例における造影剤注入と新生物の因果関係を支持する所見を得た。肝臓および脾臓の曝射線量は、それぞれ10,600rem および48,200 remであつた。

## Introduction and Background

Thorium dioxide preparations were first introduced clinically some 38 years ago<sup>1)2)</sup>, and eventually became rather widely used for a variety of roentgenographic procedures, the most popular of which were hepatolienography and cerebral angiography. The properties, uses and fates of this material have been discussed in detail<sup>3)4)5)6)</sup>. Compounds frequently used were colloidal suspensions containing 25% by volume of thorium dioxide, 20% dextrin with 0.15% methyl-p-hydrobenzoate as a preservative, and marketed as Thorotrast and Umbrathor for intravenous and oral use, respectively. Administered intravenously, it was deposited in the reticuloendothelial system, principally liver and spleen, where radioactive effects were exerted mainly by alpha rays (90%), and to a lesser extent, beta and gamma components (10% and 1%, respectively).

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Early warnings concerning possible damaging effects were based on laboratory studies and clinical use<sup>7)8)9)10)11)</sup> as these materials were found to have potent radioactive properties<sup>12)</sup>. Other early reports of clinical use<sup>13)14)</sup>, and the fact that small quantities of these radioactive materials were excreted<sup>15)</sup> were reassuring and somewhat encouraging to many to continue use of these compounds clinically.

In 1947, the first neoplasm attributable to the clinical use of Thorotrast was reported<sup>16)</sup>, and additional cases have been summarized since<sup>17)18)</sup>. There was doubt about a cause-effect relationship in some of these<sup>19)</sup>. Though such relationship cannot always be demonstrated, the same carcinogenic effects can be assumed to occur in humans as in laboratory animals, and there is general agreement that thorium dioxide media are truly hazardous. The slow increase of radioactivity to achieve equilibrium between parent and daughter materials following injection<sup>20)</sup>, and the fact that individuals who received them usually did not live beyond the latent period required to develop tumors<sup>21)</sup>, probably are reasons why more neoplasms attributable to these compounds have not been detected.

Besides causing neoplasms in organs and tissues where selectively absorbed, thorium dioxide extravasated at injection sites has caused incapacitating deformities<sup>22)23)24)</sup> requiring surgical alleviation. Granulomatous lesions have been reported<sup>25)26)27)</sup> following extravasation clinically and sarcomas have developed from thorotrast-induced fibromas in laboratory animals<sup>6)</sup>. Aplastic anemia<sup>28)29)</sup> has also been attributed to thorium dioxide administration.

In cases of neoplasms following thorium dioxide injections, certain criteria should be fulfilled to support a causal relationship: (1) thorium dioxide particles must be demonstrated in the vicinity of the tumor, (2) there must have been a sufficient latent period for development of a neoplasm, and (3) a sufficiently high dose must have been received by the tissues involved<sup>18)</sup>. However, the chemical toxicity of thorium dioxide as a carcinogen still remains to be disproved, and some tumors have been reported within a relatively short period after its administration.

Certain factors complicate determination of dose to the tissues. Time lapse since preparation of the compound<sup>6)</sup>; its distribution in tissues and organs; migration from one body site to another; uneven distribution in tissues and organs with consequent self absorption of energy and dose variations and/or excretion from the body<sup>30)31)32)33)</sup>; and time lapse from death until tissue analysis<sup>34)</sup> all are important factors in dose determinations. Assumptions are necessary in determining tissue dose, but estimates are nevertheless very useful. A variety of methods may be used<sup>30)31)32)33)34)35)</sup>.

### Case Report

A 47 year old Japanese male, received a wound of the right side of the neck twenty-six years prior to the present hospital admission, and three years later, a right internal carotid aneurysm was diagnosed using an unknown quantity of thorium dioxide-containing compound for angiography. Three right cervical operative procedures were performed, followed by residual paralysis and hypesthesia of the right arm. The patient was in good health until June, 1964, when he developed increasingly severe intermittent, dull low back pain. There was a mass in the epigastrium and enlarged left cervical lymph nodes, but an upper gastrointestinal series was essentially negative. Cervical node biopsy October, 1964 revealed adenocarcinoma. <sup>60</sup>Co teletherapy was administered, with air doses of 2,000 R to the abdomen and 4,000 R to the left cervical region. Low back pain persisted; anorexia and rapid weight loss followed. Several days prior to admission, the patient developed a hydrocele and bilateral hydrothorax. Several

times, 500–600 cc of fluid each were removed from the pleural and abdominal cavities, but cytology was not performed on these aspirates.

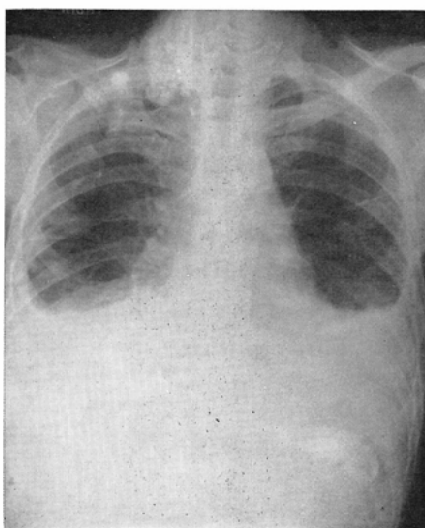
The patient was admitted to the Atomic Bomb Casualty Commission (ABCC) ward November 5, 1964. He appeared normally developed, but emaciated and chronically ill. He complained of dyspnea and low back pain. The skin was dry and dark, especially around the neck and mid-abdomen. Vital signs were normal. The right clavicle had been excised. A hard mass involved the right cervical and supraclavicular regions. Enlarged lymph nodes were palpable in the left cervical, left axillary and in the deep umbilical regions. There was a 5 cm mass in the right epigastrium continuous with the liver; fluid distended the scrotum, and there was bilateral 3+ edema of the legs. Hypesthesia and impairment of active and passive movement of the right upper extremity were noted.

### Hospital Course

On admission the red and white blood counts were normal; platelets numbered 150,000. Total protein was 3.3; albumin, 1.9; globulin, 1.4; serum glutamic oxalic transaminase 41; alkaline phosphatase, 14.39 Bodansky units; cephalin flocculation, 2+ in 24 hours. Serum phosphorus was 2.62 and chlorides 88 me/l. Urinalysis revealed 2–3 white blood counts and 300 red blood count per high power field.

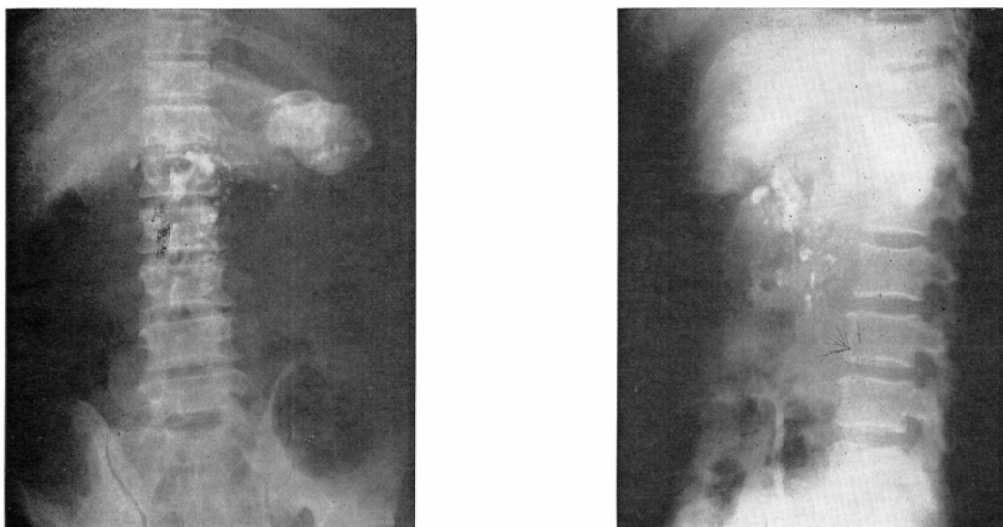
Chest and lumbosacral spine roentgenograms revealed a bilateral pleural effusion, a left lower cervical mass, and retained Thorotrast in the right cervical region and abdomen (Figs. 1a–1b).

Fig. 1a. Posteroanterior chest roentgenogram showing a bilateral pleural effusion, left lower cervical mass, and retained Thorotrast in the right cervical region and abdomen.



Widespread carcinomatosis was suspected, and treatment included 5 fluorouracil and prednisone. Leukopenia developed (1,150 WBC) which was partially corrected by blood transfusions. Pleural fluid contained many malignant cells. Intermittent hematuria and dysuria, dysphagia and low back pain continued, and the patient expired on the thirteenth post-admission day.

Fig. 1b. Anteroposterior and lateral lumbosacral spine roentgenograms showing retained Thorotrast in the liver, spleen, perigastric and portal regions.



### Autopsy

At autopsy (#64-AH-286) there was a mass 3 cm in greatest dimension in the right cervical region, and numerous 2.5 cm nodular masses elsewhere in both cervical and supraclavicular regions, and in the right breast. One thousand cc of fluid was found in the peritoneal cavity, and 200 cc and 500 cc in the right and left pleural cavities, respectively. There were many 0.5 cm tumor implants in each pleural space, on the peritoneum and mesentery. Numerous metastatic foci and slight Thorotrast deposition were present in all lobes of both lungs. The spleen was markedly atrophic, weighing 50 g, with a thick fibrous capsule, numerous small tumor foci, and massive Thorotrast deposition throughout. The liver weighed 1,050 g, was cirrhotic, the left lobe atrophic, containing extensive Thorotrast deposits, and tumor in all lobes, especially the left lobe. The tumor was identified as bile duct carcinoma, originating in the right lobe of the liver. The left kidney was grossly normal. The right kidney contained metastatic tumor throughout its cortex. Metastatic tumor was also found in the diaphragm, and in paraaortic and paracaval lymph nodes. No tumor was found about the nerve roots. Moderate Thorotrast deposition was identified in both femurs, the ribs, sternum and vertebrae; slight Thorotrast deposition was present in the pancreas, both adrenals and testes.

### Radiography

Fresh 1.5 cm in thick sections of liver and spleen are shown roentgenographically. Patchy densities represent fibrosis and deposits of thorium dioxide particles. The deposits appear more uniform in spleen than liver, and this was confirmed histologically and autoradiographically (Fig. 1c).

### Autoradiography

Sections of liver and spleen 5  $\mu$  thick produced the autoradiograms, utilizing a stripping method (EM Type ET-2E, 15 microns), and Fuji autoradiographic plates. Alpha tracks and tumor cells are shown

Fig. 1c. Radiograph of liver and spleen containing thorium dioxide.

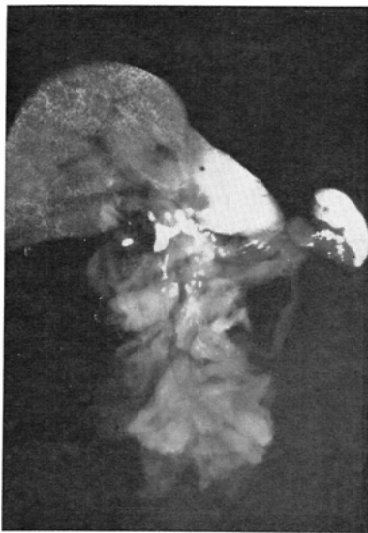
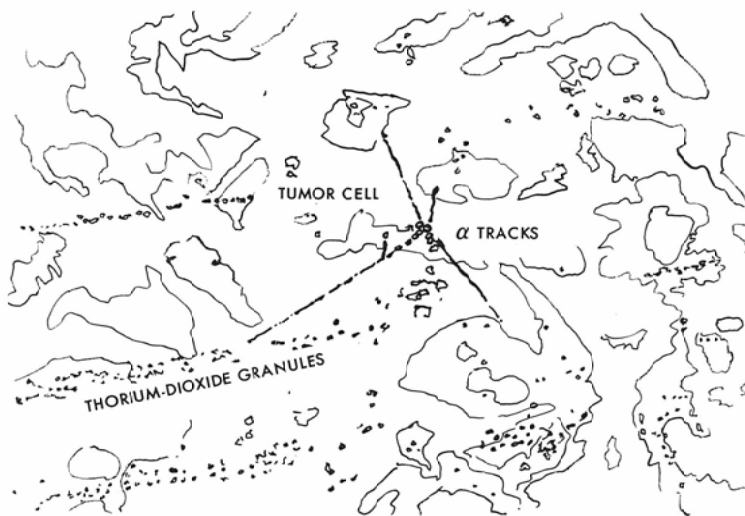
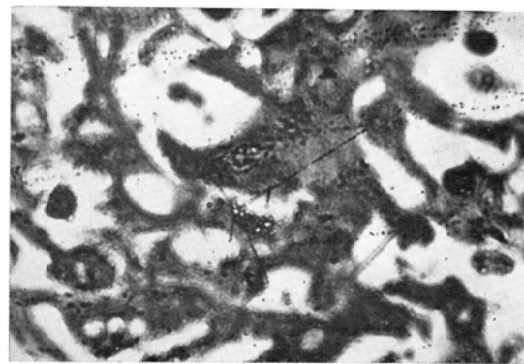


Fig. 2. Autoradiograph of liver specimen showing tumor cells and alpha tracks.



in Figure 2.

### Chemical Analysis

According to Ishibashi and Azuma's method<sup>86)</sup>, ashed samples of organs were acidified and dissolved, and the thorium precipitated by centrifugation. The precipitate was analyzed colorimetrically. Results are shown in Table I.

The wet liver and spleen specimens weighed 1,050 g and 50 g, respectively. Chemically there were 25.2 mg of thorium per gram of spleen; 5.6 mg of thorium per gram of liver; and 40.8 mg of thorium per gram of neck tissue. Total thorium in the spleen was 1.26 g; that in the liver, 5.88 g, assuming homogenous distribution. However, the quantity injected is not known. Therefore, the percent of the original

Table I Scintillation counter and chemical analysis data

Sample	Weight (g)	Scintillation Counter Study		Chemical Analysis	
		cpm <sup>1</sup>	Thorium Dioxide (mg)	Thorium Dioxide mg/g Tissue	Thorium Dioxide ( $\mu$ Ci)
Spleen	50	2,220	20.2	25.2	$2.8 \times 10^{-3}$
Liver	1,050	600	5.5	5.6	$6.2 \times 10^{-4}$
Neck Tumor		4,990	45.4	40.8	
0.025ml Thorotrast (Standard)		693			

<sup>1</sup>Background subtracted.

injected volume this residual represents is unknown. Total thorium in the neck specimen containing tumor was not determined because the tumor apparently was not confined to the excised material. The amount of thorium in the spleen was calculated to be  $0.14 \mu\text{Ci}$ ; that in the liver,  $0.65 \mu\text{Ci}$ .

Dose (rem) was obtained by the following formula<sup>37)</sup>:

$$\text{Rem} = \frac{\left( \frac{\text{effective } (\mu\text{Ci thorium (time in (erg/MeV) (disintegrations/sec./}\mu\text{Ci) energy) per organ) sec.}}{100} \right)}{\text{organ weight in grams}}$$

using an effective energy of 41 MeV<sup>38)</sup>, and twenty-three years time ( $7.1 \times 10^8$  seconds). Dose to the spleen was 48,200 rem, dose to the liver, 10,600 rem.

### Scintillation Counter study

Using a thorium standard of 0.025 ml (Thorotrast, Heyden Chemical Corporation, New York; 12 cc vials, lot # 172-1), and a well scintillation counter (Atomic, Model 1016A), the activity in splenic, hepatic and cervical specimens was determined.

As shown in Table I, thorium dioxide per gram of liver and spleen were 5.5 mg and 20.2 mg respectively by scintillation counter. Radioactivity of daughters in organs was not estimated.

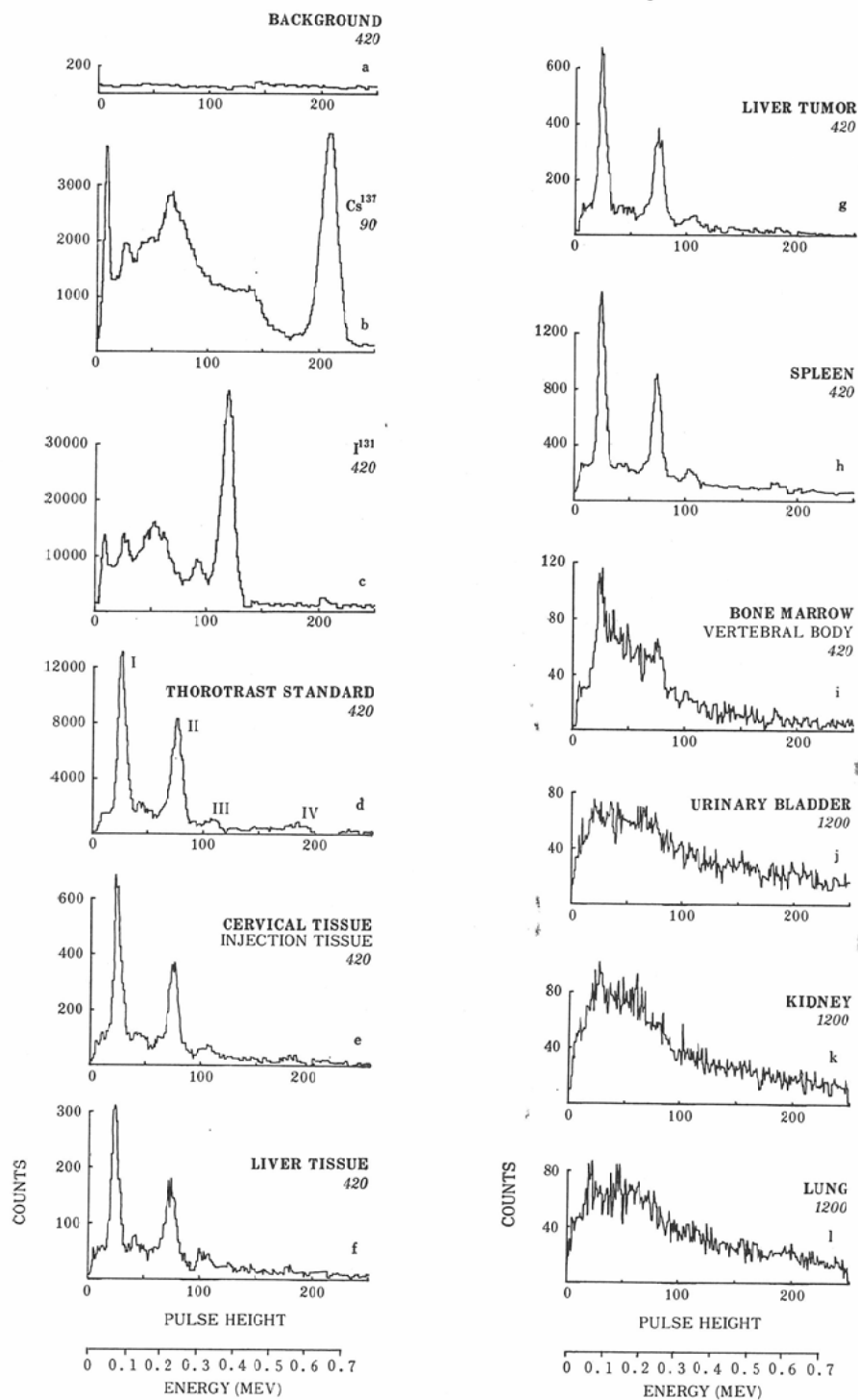
### Spectral Analysis

To determine the nuclide present in various tissues and organs, they were assessed for the gamma ray energies of the radioactive materials they contained, using a scintillation detector. These scintillation studies were not used to quantitate the radioactive material. The tissues so studied were: (1) from cervical injection site, (2) portions of tumor in or adjacent to liver, (3) a portion of liver grossly free of tumor, (4) spleen, (5) lung, (6) kidney, (7) urinary bladder, and (8) bone marrow.

A 512 channel pulse height analyzer (Toshiba Co., Ltd., Model #EDS-34204), and a well-type gamma ray scintillation detector (Atomic Instrument Co., Model 810) with a 2 inch NaI crystal, were used. Formalin-fixed samples in glass receptacles were inserted into the chamber of the scintillation detector. Without altering geometrical conditions or the circuit amplification rate, counting time (live time) was adjusted reciprocally according to the intensity of radioactivity in each specimen.

Figure 3a shows the background count, without a definite spectrum; Figure 3b, the gamma spectrum of <sup>137</sup>Cs; Figure 3c, that of <sup>131</sup>I. The relation between pulse height and gamma ray energy was determined using the 0.663 MeV peak of <sup>137</sup>Cs (Fig. 3b), three <sup>131</sup>I peaks of 0.364 MeV, 0.284 MeV, and 0.080

Figs. 3a-3l. Spectral analysis of tissues and organs.



ITALICS: LIVE TIME IN SECONDS



MeV, and the 0.163 MeV peak of  $^{131}\text{Xe}$  (Fig. 3c). Using the pattern of gamma rays of the standard (Fig. 3d), the pulse height zero point did not correspond to the energy zero point, but the energy zero point was assumed correct.

Gamma ray energy of the Thorotrast was analyzed and its spectrum established as a standard for the thorium and its daughter nuclides. In Figure 3d, there are two distinct peaks (I and II) and two relatively indistinct peaks (III and IV). Peak I with a pulse height of 30 corresponds to 0.084 MeV of  $^{228}\text{Th}$ ; peak II with a pulse height of 80 corresponds to 0.239 MeV of  $^{212}\text{Pb}$ , or 0.241 MeV of  $^{224}\text{Ra}$ . The relatively indistinct peak III at a pulse height of 110 corresponds to 0.338 MeV of  $^{228}\text{Ac}$ ; peak IV with a pulse height of 185 corresponds to 0.582 MeV of  $^{208}\text{Tl}$  and/or 0.590 MeV of  $^{228}\text{Ac}$ . The gamma spectrum of each sample so determined was compared with the spectrum of the Thorotrast standard.

The spectra for tissue near the thorium dioxide injection site, liver tissue, liver tumor, spleen, vertebral marrow, urinary bladder, kidney, and lung are shown in Figures 3e through 3l, respectively. Patterns for the cervical tissue, liver tissue, liver tumor and spleen coincided exactly with those of the standard shown in Figure 3d. The gamma ray of  $^{212}\text{Pb}$  is responsible for peak II. Whether the deposit of the daughter nuclide of  $^{228}\text{Th}$ ,  $^{212}\text{Pb}$ , was appreciable in these specimens was not established. Since these determinations were made five days following removal of specimens from the body, accumulation of daughter elements may have been insufficient to establish a ratio as existed in the old Thorotrast standard.

Figure 3i shows peaks of 0.084 MeV and 0.24 MeV in the spinal marrow specimen. Since some daughters of the thorium are "bone-seekers", and since some trabecular structures were probably included in the tissue analyzed, results obtained may not be due entirely to retained material in the marrow. No thorium spectrum was detected in the specimens of urinary bladder, kidneys or lungs (Figs. 3j-3l); their counts approximated background for 1,200 seconds. Therefore, either thorium and its daughter nuclides were not present in these particular organ specimens, or if they were, their amounts were too small to be detected.

### Discussion

Calculation of dose to organs and tissues in which thorium dioxide has been deposited is inaccurate because of time lapse following its manufacture, its distribution and migration in tissues after injection, lack of homogeneity of deposits and resulting self absorption of energy, partial excretion from the body and time lapse from removal of specimens until their analysis.

It is useful to identify retained material and to make dose estimates to tissues not merely for academic reasons, but to link thorium dioxide-containing media and neoplasms causally. In the Japanese, bile duct carcinomas predominate; whereas in the United States and Europe, the parenchymal cell tumors are more frequent. In this case, the time of injection and its purpose were reasonably well documented. Thorium dioxide was identified radiographically, autoradiographically, chemically and spectrometrically. Alpha tracks and thorium dioxide granules were identified by autoradiography near the malignant cells.

Dose to liver and spleen were estimated to be 10,600 rem and 48,200 rem respectively. Criteria<sup>18)</sup> to relate neoplasms to injected thorium dioxide were well fulfilled.

Footnote: In an oral report several points of certain histological interest and staining techniques were exemplified by specimens for this and two other patients<sup>39)</sup>.

### Summary

Findings concerning a 47 year old Japanese male who received thorium dioxide media for angiography twenty-three years prior to death from cholangiocarcinoma are described. Analysis of various autopsy specimens radiographically, autoradiographically, spectrometrically, chemically, and by scintillation counting, confirmed the presence of the media in liver, spleen, and cervical tissue, and supported a cause-effect relationship between the injected material and the neoplasm in this case. Doses to liver and spleen were 10,600 rem and 48,200 rem respectively.

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