PRIMARY LIVER CELL CARCINOMA 24 YEARS AFTER INTRAVENOUS INJECTION OF THOROTRAST

BY

A. D. MORGAN, W. H. W. JAYNE, AND D. MARRACK

From the Westminster Hospital, London

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Thorium dioxide, when injected intravenously, is taken up by the reticulo-endothelial system and retained indefinitely, rendering the liver and spleen radio-opaque (Radt, 1930). A 25% colloidal solution of thorium dioxide was marketed under the name of "thorotrast" and used not only for hepatolienography but for retrograde pyelography, bronchography, and angiography generally, not to mention other uses, e.g., cerebral ventriculography, arthrography, mammography, dacrocystography, antral visualization.

From the outset its tumour-forming potentialities were recognized (Stewart, Einhorn, and Illick, 1932), and the American Medical Association (1932) recommended that intravenous administration be discontinued, but for some years "thorotrast" was used by those who held that its radioactive properties were negligible. The conflicting claims were reviewed by Rigler, Koucky, and Abraham (1935) and by Orr, Popoff, Rose-dale, and Stephenson (1938).

Injected into animals, "thorotrast" induces sarcomata after a latent period (Roussy, Oberling, and Guerin, 1934; Selbie, 1936). By means of the Geiger counter Taft (1937a) was able to show that the standard dosage for human hepatolienography (75 ml.) gives a gamma radiation equivalent to 1.37 micrograms of radium.* Reeves and Stuck (1938) observed that retention of "thorotrast" in the reticulo-endothelial system affords a continuous opportunity for the damaging effects of alpha radiation. These rays have a higher relative biological efficiency than beta or gamma rays, and their activity is extremely localized. The emission of alpha particles in rabbits injected with "thorotrast" was studied under the spinthariscopes by Orr *et al.* (1938).

*Radium and its first two daughter isotopes emit α particles like thorium. The proportion of γ -emitting daughter isotopes in the decay products of radium and thorium to the primary isotope is sufficiently close to justify this type of comparison. The International Commission on Radiological Protection, 1954, advises that the maximum safe total body burden of radium is 0.1 microgram.

Some comfort was taken from the finding of Stenstrom and Vigness (1940) that although the "thorotrast" is retained in the tissues indefinitely, there must be some diminution of radioactivity, since radioactive elements can be demonstrated in the faeces, urine, and breath. And in a 10-year follow-up of 286 cases Yater and Coe (1943) found "no immediate or remote ill-effects of importance" in the survivors.

In 1947 MacMahon, Murphy, and Bates described a case of endothelial-cell sarcoma of the liver in a woman aged 58, 12 years after hepatolienography had been performed in the investigation of gummatous hepatitis. Since then other cases of malignancy following the injection of "thorotrast" have been published (Tables I and II). Not all the injections were intravascular (see Table I), but it was always possible to demonstrate

TABLE I
MALIGNANT TUMOURS DEVELOPING AT SITE OF THOROTRAST INJECTED EXTRAVASCULARLY

Author	Year	Sex	Age	Mode of Thorotrast Injection	Condition for which Thorotrast was Injected	Latent Period in Years	Type of Tumour
Zollinger	1949	M	64	Retrograde pyelography	Hydro-nephrosis	16	Spindle-cell sarcoma of renal pelvis
Rudolphi	1950	M	51	Dacrocystography	Dacrocystitis	35	Squamous cell carcinoma of lower eyelid
Hofer	1952	F	64	Antral visualization	Chronic sinusitis	10	Squamous cell carcinoma of antrum
Vögtlin and Minder	1952	M	47	Bronchography	Bronchiectasis	18	Squamous cell carcinoma of bronchus
Plenge and Krückemeyer	1954	F	54	Cerebral angiography	Suspected intracerebral disease	6	Sarcoma at site of injection
Gros <i>et al.</i>	1955	M	36	Antral visualization	Non-medical reasons	15	Squamous cell carcinoma of antrum

TABLE II
MALIGNANT TUMOURS DEVELOPING IN LIVER, SPLEEN,
OR BONE MARROW AFTER INTRAVASCULAR INJECTIONS
OF THOROTRAST

Author	Year	Sex	Age	Mode of Thorotrast Injection	Condition for which Thorotrast was Injected	Latent Period in Years	Type of Tumour
MacMahon <i>et al.</i>	1947	F	70	Hepato-lieno-graphy	Gumma of liver	12	Endothelial-cell sarcoma of liver
Horta	1953	F	?	Cerebral angio-graphy	Cerebro-vascular accident	3½	Endothelial-cell sarcoma of liver
Lüdin	1953	F	63	Arterio-graphy	Vascular disease of leg	14	Haemangio-endothelioma of liver and spleen
Matthes . .	1954	F	54	Hepato-lieno-graphy	Jaundice	21	Primary carcinoma of liver
Heitmann	1954	M	39	Hepato-lieno-graphy	Echino-coccal cysts of liver	20	Carcinoma of common bile duct
Tesluk and Nordin	1955	M	68	Cerebral angio-graphy	Suspected cerebro-vascular disease	6	Haemangio-endothelioma of liver
Fruhling <i>et al.</i>	1955	M	49	Arterio-graphy	Vascular disease of leg	12	Haemangio-endothelioma of liver, spleen, and bone marrow
Grossiord <i>et al.</i>	1956	M	54	..	Osteomyelitis of femur	21	Adenocarcinoma of liver
Roberts and Carlson	1956	F	45	..	Arterio-venous fistulae of leg	17	Carcinoma of hepatic duct
Horta . .	1956	M	46	? Aorto-graphy	Unknown	22	Haemangio-endothelioma of liver
Present case	1958	F	48	Hepato-lieno-graphy	Upper abdominal pain	24	Hepatoma of liver

a considerable quantity of "thorotrast" at the site of the subsequent tumour.

The case of Abrahamson, O'Connor, and Abrahamson (1950), who reported bilateral carcinoma of the lungs 16 years after hepato-lienography, has been purposely omitted. At necropsy there was little "thorotrast" in the lungs, and the evidence that malignancy was in any way connected with the injection is very slight. A similar case was reported by Lloyd (1957). These cases are clearly different from that of Vögtlin and Minder (1952), where the tumour arose in the vicinity of large amounts of "thorotrast" left in the lung from an earlier broncho-graphy.

In a recent review Horta (1956) rejected the case of Heitmann (1954) on the grounds that the bile-duct carcinoma did not arise near the "thoro-

trast" deposits in the liver. Roberts and Carlson (1956), reporting a similar case, stressed the concentration of "thorotrast" in the portal lymph nodes and their proximity to the bile ducts. We have therefore included both cases. However, we share Horta's reservations over the case of Grossiord, Roucayrol, Duperrat, Ceccaldi, and Meeus-Bith (1956), since their patient also had cirrhosis of the Laennec type, thus affording a stimulus to neoplasia other than radioactivity alone.

More exacting criteria are demanded by Guimaraes, Lamerton, and Christensen (1955), who question the cases of MacMahon *et al.* (1947), Zollinger (1949), and Rudolphi (1950), on the grounds that pre-existing inflammatory conditions (gummatous hepatitis, chronic pyelonephritis, dacrocystitis) may also have been factors in producing malignancy later, and by this token one would have to demur in accepting the cases of Hofer (1952) and Vögtlin and Minder (1952) as well, since each gave a history of antecedent inflammation at the site of the neoplasm.

The tables also omit, in view of inadequate data, three unpublished cases mentioned by Thomas, Henry, and Kaplan (1951) and four others referred to by Looney and Colodzin (1956).

The case recorded below seems to fulfil all the requirements of post-irradiation malignancy—a primary liver-cell carcinoma occurring in the absence of cirrhosis or pre-existing inflammation, 24 years after the intravenous administration of "thorotrast."

Case History

The patient, a woman aged 48, was admitted to hospital on April 5, 1956, because of abdominal pain, first noticed in November, 1955, when it appeared at the beginning of a normal menstrual period. At this time it was situated in the epigastrium and right loin and was described as being very severe. After a week's rest in bed, she recovered completely. Four days before admission she noticed generalized abdominal pain which again coincided with the onset of menstruation. This pain soon became localized to the epigastrium, but was also referred to the tip of the right shoulder and was aggravated by coughing and deep breathing.

In 1932, when she was 24, she was investigated at another hospital for an upper abdominal condition by the injection of some material into an arm vein (the exact dosage is unknown), followed by a number of radiographs of the abdomen. This must have been the occasion when the "thorotrast" was administered, since she had had no other injection.

On examination she looked ill and had obviously lost weight. At the time of her first admission, the

epigastrium was very tender, with marked guarding which at first prevented the palpation of an underlying mass. Later it became possible to feel a hard, irregular epigastric mass which moved on respiration.

The following investigations were carried out :

A radiograph of the abdomen showed radio-opacities in the liver, spleen, and lymph nodes, especially those of the pre-aortic group, the pattern being characteristic of hepatolienography by "thorotrast" (Fig. 1).

An oral cholecystogram was normal.

A barium meal showed a smooth pressure defect related to the whole of the lesser curve of the stomach. The appearances were similar to those produced by a large pancreatic cyst.

A blood count gave : haemoglobin 90%, W.B.C. 11,000 per c.mm. (neutrophils 88%, lymphocytes 8%, monocytes 4%).

Serum amylase was less than 100 units. Tests for occult blood were negative. Serum bilirubin (direct) was 0.1 mg.% and (indirect) 0.1 mg.%, total 0.2 mg.%. Flocculation tests gave : thymol turbidity, 0 units, thymol flocculation, 0 units, serum colloidal gold, 0 units, zinc sulphate turbidity, 1 unit.

In view of the concentration of "thorotrast" shown by the radiographs, a diagnosis of primary carcinoma of the liver was suspected. Laparotomy was undertaken, and the abdominal tumour was found to be a large liver riddled with hard white areas looking not unlike secondary deposits ; careful examination of the abdominal contents failed to reveal a primary growth. A biopsy taken from the liver showed a carcinoma with a trabecular structure suggesting hepatic origin. The adjacent liver tissue contained "thorotrast" granules (Fig. 2).

The patient made a good recovery from her operation and was discharged from hospital on the fourteenth day after operation. Thereafter, her condition gradually deteriorated and she died at home on August 30, 1956.

FIG. 1.—Radiograph of upper abdomen showing radio-opacity of liver, spleen (with splenunculus), portal and pancreatico-splenic lymph nodes.

FIG. 2.—Biopsy of liver showing margin of carcinomatous nodule and "thorotrast" deposits (centre). Haematoxylin-eosin $\times 160$.

Necropsy Report

The subject was emaciated and dehydrated. The brain, buccal cavity, upper respiratory passages, and thyroid gland were normal. The immediate cause of death was bilateral bronchopneumonia, and both lungs were riddled with metastatic carcinomatous deposits 1–2 mm. in diameter. A few of the mediastinal lymph nodes were invaded by growth. The heart showed brown atrophy ; the aorta and main branches were healthy. There was mild varicosity of the lower oesophageal veins.

The peritoneal sac contained several pints of sero-fibrinous fluid. The liver was enlarged (79 oz.) and riddled with malignant deposits. It was not possible to determine the precise site of origin, but the right lobe was largely destroyed by confluent tumour masses, and was, if anything, reduced in size ; while the left lobe appeared to be enlarged, and contained discrete deposits up to 2 cm. in diameter (Fig. 3). There was no evidence of underlying cirrhosis.

The gall bladder and bile ducts were healthy, but in the portal fissure lay a group of yellowish discrete nodules, bony hard in consistency, resembling calcified hepatic lymph nodes. Similar nodules $\frac{1}{2}$ –1 cm. in diameter lay along the anterior aspect of the pancreas

FIG. 3.—Anterior and cut surfaces of liver showing a confluent growth in the right lobe, discrete nodules in the left lobe.

and were taken to be the pancreatico-splenic lymph nodes.

The spleen was hard and shrunken (1 oz.), with a thick white capsule. The cut surface presented a remarkable appearance, the malpighian bodies being greatly enlarged and bright yellow, their colour contrasting sharply with the dark red of the pulp (Fig. 4). The splenic artery was normal.

There was a small carcinomatous deposit in each kidney—the only extrahepatic metastases in the abdomen. The pancreas, adrenals, and pelvic organs were normal, and the only other finding of note was congenital shortening of the jejunum and ileum to about one half of the usual length.

Histology

Liver.—The tumour was similar to that reported following biopsy, i.e., a primary carcinoma of the "hepatoma" type, the tumour cells occurring in short columns, with occasional attempts at acinar formation. The surviving liver parenchyma had a normal lobular pattern, and there was no real evidence of cirrhosis, although the portal canals and central veins showed a definite excess of fibrous tissue, anatomically related to the distribution of "thorotrast" (Figs. 5, 6). This was in the form of a grey, isotropic, granular material, partly extracellular but mostly contained in macrophages and conspicuously absent in the tumour tissue (Fig. 7). Liver cell degeneration, where present, was not anatomically related to the "thorotrast."

Spleen.—The yellow colour of the malpighian bodies proved to be due to massive deposits of "thorotrast" (Figs. 8, 9). Under higher magnification this was observed as an aggregation of small rounded granular clumps, each of which owed its outline to the limiting membrane of a macrophage cell, although it was rarely possible to demonstrate the nucleus. The sharp circumscription of the deposits was exaggerated by an almost total depletion of malpighian lymphoid tissue, and a general atrophy of the red pulp.

Lymph Nodes.—The hepatic and pancreatico-splenic groups required prolonged treatment with a decalcifying agent before they could be sectioned. The lymphoid tissue was completely replaced by dense fibrous tissue incorporating large quantities of extracellular "thorotrast," except at the hilum, where the transfer of granules by macrophage cells appeared to be still active (Fig. 10). There were no metastases in these nodes.

Bone Marrow.—A random sample from the humeral shaft revealed aggregates of macrophages containing "thorotrast," but the quantities were less than in the liver, spleen, and lymph nodes. The haemopoietic cells in the immediate vicinity showed no abnormality (Fig. 11).

Lungs.—Sections confirmed the presence of blood-borne metastases and of terminal bronchopneumonia. No "thorotrast" was observed.

Distribution and Radioactivity of Thorotrast

Radiography of the liver and spleen after death showed abundant radio-opaque material in each. In the liver this was in the form of a fine tracery, presumably corresponding to the lymphatic pathways in the portal canals; concentration in the spleen was denser and coarser (Fig. 12).

Autoradiographic Studies.—Analyses of the amount and kind of radioactive substances present and the distribution of radiation dose were kindly conducted by Professor Rotblat and Dr. Ward, of the Physics Department at St. Bartholomew's Hospital Medical College, using α -track autoradiographs. Sections of liver, spleen, lymph node, and bone marrow were cut at $5\ \mu$ and coated with a layer of C2 nuclear research emulsion in liquid form (Rotblat and Ward, 1956a). Observations were made of the lengths of the α -particle tracks, of the numbers of tracks from unit volume of the sections recorded in unit time, and of the distribution and size of the "thorotrast" aggregates (Fig. 13). Over 14,000 tracks were studied, the method of analysis being that described by Rotblat and Ward (1956b) and Rotblat (1957). The average tissue dosage is given in Table III, the calculations

TABLE III
AVERAGE TISSUE DOSAGES

Tissue	Average Tissue Dosage (rads per wk.)	Dose from Largest Aggregates (rads per wk.)	Dose from Groups of Aggregates (rads per wk.)	Cumulative Average Dose (rads)
Liver	0.062	8.3	3.2-7.7	1,250
Spleen	0.51	12.4		3,600
Bone marrow ..	0.32	2.2	3.5	
Lymph node ..	2.2	31.0		

being based on the assumption that all the energy released as α -particles was dissipated uniformly throughout the tissue, i.e., it does not allow for variations in the dose in different parts of the organ. The effect of aggregation in the various tissues is discussed below.

Liver.—The aggregates were grouped in small areas of the tissue which appeared to be unrelated to the invading cancer tissue. From a study of seven such groups it was found that 6% of the tissue was receiving a dose varying from 3 to 8 rads per week. As well as these groups, there were a number of single small aggregates scattered throughout the tissue, which would produce a small approximately uniform dose of 0.00121 rads per week. The largest single aggregate in the tissue examined was 145 microns in radius and the dose in the surrounding 50 microns was 8.3 rads per week.

Spleen.—Almost all the activity was concentrated in the malpighian bodies, which were regarded as spheres of radioactive material of radii varying from 0.1 to 1.65 mm. These deposits would irradiate the surrounding layer of tissue 0.05 mm. thick with a dose of 8.0 to 12.4 rads per week. Within the

FIG. 4

FIG. 4.—Spleen showing yellowish deposits of “thorotrast” at site of malpighian bodies.

FIG. 5

FIG. 5.—Photomicrograph of liver showing fibrous increase in portal canals related to “thorotrast” deposits. Haematoxylin-eosin $\times 90$.

FIG. 6

FIG. 6.—Fibrous increase round centrilobular vein related to “thorotrast” deposits. Haematoxylin-eosin $\times 90$.

FIG. 7.—Macrophages in portal canals containing "thorotrast."
Haematoxylin-eosin $\times 500$.

FIG. 8.—Low-power view of spleen showing discrete masses of
"thorotrast." Haematoxylin-eosin $\times 8$.

FIG. 9.—Higher magnification to show "thorotrast" deposited round penicillar artery with depletion of
lymphoid tissue. Haematoxylin-eosin $\times 45$.

FIG. 10

FIG. 11

FIG. 10.—Lymph node showing fibrous replacement of lymphoid tissue. Intracellular "thorotrast" near hilum. Haematoxylin-eosin $\times 40$.

FIG. 11.—Bone marrow showing "thorotrast" in macrophages. Haematoxylin-eosin $\times 300$.

FIG. 12.—Radiograph of liver and spleen after removal from the body (natural size).

FIG. 12

FIG. 13.—Photomicrograph of "thorotrast" aggregates in liver, showing α -tracks. (By courtesy of Professor J. Rotblat.)

malpighian bodies, the "thorotrast" was concentrated in smaller aggregates about 0.005 mm. in radius packed more or less closely together. In the less dense regions the tissue spaces were subject to a dose of 6.8 rads per week.

Lymph Node.—All cells were irradiated with a dose of at least 0.32 rads per week with many cells receiving doses of 19 to 31 rads per week from large aggregates 0.09–1.31 mm. in radius.

Bone Marrow.—All cells were irradiated with a dose of 0.17 rads per week with a few spots of higher dosage up to 3.5 rads per week.

The activity observed in the tissue sections indicated that a considerable proportion of the soluble daughter isotopes of thorium were being removed from the organs during life, the percentage of the total α -particle activity retained being only about 30% in the spleen, liver, and bone marrow and 50% in the lymph node. A rough estimate of the thorium content of the spleen and liver, obtained from the specific α -particle activity of the tissues, was 3.5 g. in each organ (Table IV), suggesting that the total volume of "thorotrast" injected into the patient was of the order of

TABLE IV
ESTIMATED THORIUM CONTENT OF SPLEEN AND LIVER

Tissue	Th Content (mg. per g.)	Mass of Organ (g.)	Total Th Content (g.)	Equivalent Volume of Thorotrast (ml.)
Liver	1.57	2,240	3.52	18.5
Spleen .. .	122	28.4	3.47	18.3
Bone marrow ..	1.10	—	—	—
Lymph node ..	175	—	—	—

40 ml. In all tissues the "thorotrast" was concentrated in aggregates of varying size, so that the radiation dose was composed of a small, approximately uniform dose from small aggregates, with foci of more intense dosage in the tissue surrounding large aggregates or groups of aggregates. However, it would seem from experimental work that the thorium was initially much more uniformly distributed in the tissues and that aggregation occurred progressively during the following years. This process affects the cumulative dose to the cells in the tissues.

Assuming that the patient was injected with 40 ml. "thorotrast," the cumulative dose over 25 years was estimated to be in the order of 3,600 rads in the spleen and 1,250 rads in the liver.

Discussion

The introduction of "thorotrast" into human tissues provides a special opportunity for obtaining data on the effects of prolonged irradiation. The standard dosage of 75 ml. employed in hepatolienography involves introducing into the body some 15 g. of thorium and its derivatives. The thorium itself is retained in the reticulo-endothelial system, but a number of its daughter isotopes, differing chemically from thorium, e.g., ^{228}Ra (MsThI), ^{224}Ra (ThX) and ^{212}Pb (ThB), are excreted from the body during the first few months (Rotblat and Ward, 1956b). These can only be distinguished from thorium (^{232}Th) by special observations on the type and energy of the radiation emitted. Since the variety and proportions of these isotopes in "thorotrast" vary with the method and length of time taken over the purification stages in its manufacture, and also on the time lapse between preparation and injection, up to 50% of the initial detectable radioactivity may be in the form of isotopes which are excreted, or their immediate precursors. As a result there may be a considerable fall in the irradiation being received by the body during the first six to 12 months after injection. This phenomenon may account for some of the differences in the biological fate of injected "thorotrast" described in the literature (Wichmann and Fricke, 1932 ;

Tripoli and Haam, 1932; Shute and Davis, 1933; Stenstrom, 1941; Schwaiger, Maier-Leibnitz, and Schmeiser, 1949).

The radioactivity of some of these daughter isotopes is greater than that of the same mass of thorium, and as a result there is considerable variation with time in the total α particle energy dissipated in the body. This energy is dissipated in the cells in the immediate vicinity of the isotope, i.e., the reticulo-endothelial system, since α particles have a very short range. If the only isotope in 75 ml. of "thorotrast" were thorium (232 Th), such energy would be in the order of 0.4 ergs/sec. initially, and theoretically be capable of increasing by a factor of 10 if the daughter isotopes formed accumulated in the tissues (Taft, 1937b; Reeves and Morgan, 1937; Rundo, 1956). Rundo found 224 Ra (ThX) and 212 Pb (ThB) in human blood many years after the injection of "thorotrast," an observation at variance with the claims of Looney, Arnold, Levi, and Jee (1955) that after 20 years there is very little further loss of radioactivity from the isotopes remaining in the body.

The radioactivity of the tissues increases after death, indicating that the "fixed" isotopes are not in equilibrium with their daughter products, presumably because the latter are soluble and are continually being eluted during life. This phenomenon, which depends on the rate of extracellular fluid exchange around the "fixed" isotopes in the aggregate (and therefore to some extent on the degree of fibrosis around them), may explain the lack of consistency in the proportions of the daughter isotopes of thorium which Rundo observed in the tissues (a) between different patients; (b) between the various organs of the same patient; and (c) between the different parts of the same organ.

The relation of fibrosis to the "thorotrast" deposits has been commented on by various authors. The appearances in the lymph nodes and spleen suggest that the degree of fibrosis may be related to the concentration of the drug. Certainly dense scarring may follow leakage of "thorotrast" into the tissues surrounding veins (Yater and Whitmore, 1938; Amory and Bunch, 1948), and in one case sarcomatous change supervened (Plenge and Krückemeyer, 1954).

The manner in which the fibrosis is produced is unsettled. Naegeli and Lauche (1933) thought that a sufficient concentration of "thorotrast" could cause cell death, followed by fibrosis, but it is not clear whether this is brought about by the physical effects of a foreign body, the chemical properties of the drug (cf. silicosis), or the radio-

activity of thorium and/or its derivatives. Rigler *et al.* (1935) regarded the fibrosis as a toxic effect rather than due to irradiation. Thomas *et al.* (1951) held the opposite view.

We incline to the belief that the fibrosis is a low-grade inflammatory response to repeated necrosis of cells within the range of the radioactive deposits. The α particles have a mean range of about 0.05 mm., and a very high specific ionization; therefore they are biologically most dangerous, since the amount of tissue injury is related to the specific ionization (Gray, 1953).

Whatever the cause of the fibrosis in the liver, there is no convincing evidence that "thorotrast" can induce cirrhosis of the Laennec type, as has been suggested by Cassel, Ruffin, Reeves, and Stoddard (1951) and Jonsell and Lindgren (1944). In experimental animals the drug causes an increase in connective tissue, but such intracellular changes that occur do not cause disturbance of the lobular architecture (Naegeli and Lauche, 1933; Tripoli, 1934) and the same appears to hold for the human liver (Jacobson and Rosenbaum, 1938; Groskopf, Bolck, and Büll, 1951; Berenbaum and Birch, 1953).

The point is of some interest, since, according to Moore (1951), about 90% of all liver-cell carcinomas and 50% of all bile-duct carcinomas occur in livers with cirrhosis. In these cases of cirrhosis it is reasonable to suppose that cellular multiplication in the surviving lobules undergoing compensatory hyperplasia is a greater factor in carcinogenesis than the mere presence of fibrous tissue. It is important to note, therefore, that the fibrous tissue increase in the portal canals and round the central veins, related to the deposition of "thorotrast" and described by many authors, is unaccompanied by disturbance of lobular architecture and unlikely to be in itself a factor in subsequent carcinogenesis.

Malignant growths of the liver following the intravascular administration of "thorotrast" fall into two broad groups: the haemangio-endotheliomata or endothelial cell sarcomata on the one hand, and the primary carcinomata of liver-cell or bile-duct origin on the other. Horta (1956) thinks that all the genuine cases have belonged to the first group, but this is to ignore the claims of Matthes (1954), Heitmann (1954), Grossiord *et al.* (1956), Roberts and Carlson (1956), and our own case. It may be of interest to record that both types of tumour have been reproduced experimentally in animals by injecting "thorotrast" (Zeithofer and Speiser, 1954; Guimaraes *et al.*, 1955).

It is still a matter of opinion whether the number of recorded cases is enough to justify the disuse of "thorotrast," if indeed the tumours are produced by irradiation at all. Bauer (1948) showed that the radiation given off by "thorotrast" is 6 r per day, which by current estimates is about 140 times the amount usually cited as the maximum daily permissible dose in regulations for protection against x rays. Yet Thomas *et al.*, writing in 1951, considered that the five malignancies recorded up to that time did not indicate the carcinogenic properties of "thorotrast" in man; and Looney (1954, 1955) considers that no significant number of clinical disorders have resulted from its use, based on a follow-up of 4,800 individuals.

The number of case records in which there has been good reason to ascribe malignancy to "thorotrast" has steadily mounted, and it is our view that this trend is likely to continue during the next few years. Furthermore, it is certain that a number of cases have gone unrecorded, where there has been no necropsy, or where the pathologist has not recognized the deposits of "thorotrast" or connected them with a new growth.

In our view primary growths arising in close proximity to deposits of "thorotrast," in the absence of other stimuli to neoplasia such as cirrhosis and chronic inflammation, can reasonably be regarded as irradiation phenomena. Until this is generally accepted it is worth while to record such cases in the medical literature.

Summary

(1) A case of primary liver-cell carcinoma occurring 24 years after the intravenous injection of "thorotrast" is described, together with the methods of assessing the residual radioactivity in the organs after death.

(2) Similar case records are critically examined.

(3) It is concluded that malignancy arising at the site of "thorotrast" deposit is likely, if there are no other predisposing factors, to be an irradiation phenomenon.

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Addendum

Since this article was submitted, several cases of malignant tumours following the use of thorotrast

have been published: Boemke (1956) described an epithelioma of the renal pelvis after retrograde pyelography; Batzenschlager and Wilhelm (1957) reported primary carcinoma of the liver 11 years after arteriography of a limb. Unfortunately there was no proper necropsy, and the possibility of a primary elsewhere was not eliminated. Federlin and Scior (1957) record a liver cell carcinoma 13 years after cerebral angiography, but the patient also had a rectal carcinoma. They also attribute an ovarian carcinoma to a salpingography 23 years earlier. Other cases of liver tumours have been reported by Caroli, Etévé, and Platteborse (1956) and Fallot (1956), but we have not been able to obtain the journal in which they appear.

REFERENCES

- Abrahamson, L., O'Connor, M. H., and Abrahamson, M. L. (1950). *Irish J. med. Sci.*, 229.
- American Medical Association: Council on Pharmacy and Chemistry (1932). *J. Amer. med. Ass.*, **99**, 2183.
- Amory, H. I., and Bunch, R. F. (1948). *Radiology*, **51**, 831.
- Batzenschlager, A., and Wilhelm, E. (1957). *Ann. Anat. path. méd.-chir.*, **2**, 39.
- Bauer, K. H. (1948). *Chirurg*, **19**, 387.
- Berenbaum, M. C., and Birch, C. A. (1953). *Lancet*, **2**, 852.
- Boemke, F. (1956). *Zbl. allg. Path. path. Anat.*, **95**, 464.
- Caroli, J., Etévé, J., and Platteborse, R. (1956). *Rev. méd.-chir. Mal. Foie*, **31**, 53.
- Cassel, C., Ruffin, J. M., Reeves, R. J., and Stoddard, L. D. (1951). *Arch. intern. Med.*, **82**, 42.
- Fallot, P. (1956). *Rev. méd.-chir. Mal. Foie*, **31**, 60.
- Federlin, K., and Scior, H. (1957). *Frankfurt. Z. path.*, **68**, 225.
- Fruhling, L., Gröcs, C. M., and Batzenschlager, A. (1955). *Bull. Ass. franç. Cancer*, **42**, 559.
- Gray, L. H. (1953). *Brit. J. Radiol.*, **26**, 609.
- Gros, C. M., Fruhling, L., and Keiling, R. (1955). *Bull. Ass. franç. Cancer*, **42**, 556.
- Groskopf, K. W., Bolck, F., and Eüll, H. J. (1951). *Fortschr. Röntgenstr.*, **75**, 34.
- Grossiord, A., Roucayrol, J. C., Duperrat, B., Ceccaldi, P. F., and Meeus-Bith, L. (1956). *Bull. Soc. méd. Hôp., Paris*, **72**, 49.
- Guimaraes, J. P., Lamerton, L. F., and Christensen, W. R. (1955). *Brit. J. Cancer*, **9**, 253.
- Heitmann, W. (1954). *Chirurg*, **25**, 223.
- Hofer, O. (1952). *Dtsch. zahnärztl. Z.*, **7**, 736.
- Horta, J. da Silva (1953). *Chirurg*, **24**, 218.
- (1956). *A.M.A. Arch. Path.*, **62**, 403.
- Jacobson, L. E., and Rosenbaum, D. (1938). *Radiology*, **31**, 601.
- Jonsell, J. E., and Lindgren, G. H. (1944). *Radiol. clin. (Basel)*, **13**, 201.
- Lloyd, O. C. (1957). Meeting of Path. Soc. Gt. Britain and Ireland, Royal College of Surgeons, London, January 4, 1957.
- Looney, W. B. (1954). *Amer. J. Roentgenol.*, **72**, 838.
- (1955). *Ann. intern. Med.*, **42**, 378.
- and Colodzin, M. (1956). *J. Amer. med. Ass.*, **160**, 1.
- Arnold, J. S., Levi, H., and Jee, W. S. (1955). *A.M.A. Arch. Path.*, **60**, 173.
- Lüdin, M. (1953). *Schweiz. Z. allg. Path., Bakt.*, **16**, 987.
- MacMahon, H. E., Murphy, A. S., and Bates, M. I. (1947). *Amer. J. Path.*, **23**, 585.
- Matthes, T. (1954). *Arch. Geschwulstforsch.*, **6**, 162.
- Moore, R. A. (1951). *A Textbook of Pathology*, 2nd ed., p. 617. Philadelphia.
- Naegeli, T., and Lauche, A. (1933). *Klin. Wschr.*, **12**, 1730.
- Orr, C. R., Popoff, G. D., Rosedale, R. S., and Stephenson, B. R. (1938). *Radiology*, **30**, 370.
- Plenge, K., and Krückemeyer, K. (1954). *Zbl. allg. Path. path. Anat.*, **92**, 255.
- Radt, P. (1930). *Med. Klin.*, **26**, 1888.

- Reeves, D. L., and Stuck, R. M. (1938). *Medicine (Baltimore)*, **17**, 37.
- Reeves, R. J., and Morgan, J. E. (1937). *Radiology*, **29**, 612.
- Rigler, L. G., Koucky, R., and Abraham, A. L. (1935). *Ibid.*, **25**, 521.
- Roberts, J. C., and Carlson, K. E. (1956). *A.M.A. Arch. Path.*, **62**, 1.
- Rotblat, J. (1957). Personal communication.
- and Ward, G. (1956a). *Phys. Med. Biol.*, **1**, 57.
- (1956b). *Ibid.*, **1**, 125.
- Roussy, G., Oberling, C., and Guerin, M. (1934). *Bull. Acad. nat. Méd. (Paris)*, **112**, 809.
- Rudolphi, H. (1950). *Beitr. path. Anat.*, **111**, 158.
- Rundo, J. (1956). *Phys. Med. Biol.*, **1**, 138.
- Schwaiger, M., Maier-Leibnitz, H., and Schmeiser, K. (1949). *Klin. Wschr.*, **27**, 311.
- Selbie, F. R. (1936). *Lancet*, **2**, 847.
- Shute, E., and Davis, M. E. (1933). *Arch. Path. (Chicago)*, **15**, 27.
- Stenstrom, W. (1941). *Radiology*, **37**, 698.
- and Vigness, I. (1940). *Proc. Soc. exp. Biol. (N.Y.)*, **44**, 18.
- Stewart, W. H., Einhorn, M., and Illick, H. E. (1932). *Amer. J. Roentgenol.*, **27**, 53.
- Taft, R. B. (1937a). *Radiology*, **29**, 530.
- (1937b). *J. Amer. med. Ass.*, **108**, 1779.
- Tesluk, H., and Nordin, W. A. (1955). *A.M.A. Arch. Path.*, **60**, 493.
- Thomas, S. F., Henry, G. W., and Kaplan, H. S. (1951). *Radiology*, **57**, 669.
- Tripoli, C. J. (1934). *Amer. J. clin. Path.*, **4**, 212.
- and Haam, E. von (1932). *Proc. Soc. exp. Biol. (N.Y.)*, **29**, 1053.
- Vögtlin, J., and Minder, W. (1952). *Radiol. clin. (Basel)*, **21**, 96.
- Wichmann, F. W., and Fricke, O. (1932). *Fortschr. Röntgenstr.*, **45**, 664.
- Yater, W. M., and Coe, F. O. (1943). *Ann. intern. Med.*, **18**, 350.
- and Whitmore, E. R. (1938). *Amer. J. med. Sci.*, **195**, 198.
- Zeitlhofer, J., and Speiser, P. (1954). *Z. Krebsforsch.*, **60**, 161.
- Zollinger, H. U. (1949). *Schweiz. med. Wschr.*, **79**, 1266.