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Epidemiology of Thorotrast-induced Hepatic Angiosarcoma in the United States

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An epidemiologic investigation of hepatic angiosarcoma (HAS) in the United States, directed primarily at the years 1964–1974, has identified 26 cases of Thorotrast-induced HAS. This study indicates that the occurrence of Thorotrast-induced HAS was still increasing in the early 1970s and that a larger proportion of the more recent cases had relatively low-dose Thorotrast procedures and a prolonged latent period. A number of cases were identified who had a history of preexisting liver disease, associated vascular malformations, or exposure to arsenic or iron; the possible role of such additional risk factors is uncertain.

INTRODUCTION

An intensive case-finding effort for hepatic angiosarcoma (HAS) occurring in the United States during the years 1964–1974 was instituted following the demonstration in early 1974 of the markedly increased risk for this rare tumor in polyvinyl chloride polymerization workers (Creech and Johnson, 1974; Lloyd, 1974). A morphologic and epidemiologic investigation of all identified cases is underway to study in greater detail the development of HAS in cases with known etiology and to look for additional etiologic factors in the remaining cases. This paper reviews the epidemiologic findings in all 26 cases of Thorotrast-induced HAS identified by our study; a companion paper by Telles *et al.* reviews the morphologic findings in these cases. By definition, cases of only nonmalignant Thorotrast-induced hepatic disease are not included here, although in the paper by Telles *et al.* we have postulated a hepatic fibrotic precursor stage to Thorotrast-induced HAS and evaluate this in detail.

METHODS

Information relating to cases of HAS was solicited by the Center for Disease Control (CDC) in a variety of ways: (a) announcements were placed in 7 medical journals; (b) a mailing was sent to all pathologists in the country; (c) separate mailings were sent to all state epidemiologists, major tumor referral centers, and statewide tumor registries; (d) a death certificate review for Code 197.8 for 1966–1973 was conducted with the assistance of the National Center for Health Statistics and the 50 state health departments; (e) arrangements were made with the

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Armed Forces Institute of Pathology (AFIP) to include approximately 80 cases in their files (1943–1975) in the review; (f) a number of cases were included from industrial surveys of vinyl chloride (VC) workers and others potentially exposed to VC; and (g) permission was requested to include the previously published cases of HAS which occurred during the years 1964–1974.

The evaluation procedure for each identified case was as follows: Initially, permission was requested to review the appropriate pathologic specimens (all non-AFIP case material submitted for review is stored at the National Cancer Institute's Laboratory of Pathology). Following confirmation of the diagnosis the local physician was notified and with his permission the nearest of kin was identified and contacted. Consent was obtained to review medical records and a questionnaire was administered by telephone to obtain detailed occupational, residential, and chemical exposure histories. In selected cases, friends, employers, previous physicians, or others were also interviewed.

As of May 1977, CDC had been notified of 327 cases. Pathologic specimens were obtained for review in 312 cases (95%); of these, 222 (71%) were confirmed as HAS, 71 (23%) were considered not to be HAS, and 21 (7%) are still under review.

Pathologic specimens were obtained for all 26 Thorotrast-induced cases (although the specimen for case No. 19 was received too late for inclusion in the companion review). A family interview was conducted for all but case No. 12. Descriptive information on Thorotrast administration was available for all cases, although precise dose data could only be obtained for 14.

Eight cases included in this review have been reported previously, primarily as case reports by the individual physicians and pathologists (Cavanagh, 1935; Curry *et al.*, 1975; Howard *et al.*, 1971; Looney, 1960; Ludwig and Hoffman, 1975; Nettleship and Fink, 1961; Rakov *et al.*, 1963; Spencer *et al.*, 1976).

RESULTS

Table 1 lists the basic epidemiologic data for all 26 cases. Of these, 20 occurred within the time span of the intensive case-finding effort (1964–1974); the remaining 6 cases, while outside the time span of the case-finding effort, were also submitted for review and are included in this presentation.

Nineteen cases (73%) were male and 7 (27%) were female; 25 cases (96%) were white, and 1 (4%) was black (case No. 20).

Three cases received Thorotrast during military service in World War II, and 1 case received an intravenous dose in a physician's office. The remaining 22 cases were distributed among 19 hospitals, with 4 cases having received Thorotrast at a single hospital.

Figure 1 depicts the occurrence of cases by year of death. In the 1964–1974 period an increasing number of cases are seen in the more recent years (this increase appears to be larger than that seen at the present time for non-Thorotrast angiosarcoma in our larger study). Figure 1 also shows that the latent period has increased from 19.8 years in the earliest cases to 28.0 years in the last group of cases. The most recent case (No. 26) had a latent period of 40 years. Another change related to date of occurrence is seen in Table 1, which shows that the procedure for which Thorostrast was given shifted from high-dose hepatolienog-

TABLE 1

EPIDEMIOLOGIC DATA FOR CASES OF THOROTRAST-ASSOCIATED HEPATIC ANGIOSARCOMA IN THE UNITED STATES

Case no.	Sex	Age at death	year of death	Age at Thorotrast administration	Year of Thorotrast administration	Latent period (years)*	Dose of Thorotrast (cc)	Route of administration	State of administration
1	F	52	1955	29	1931	23	72	Hepatolienography	D.C.
2	M	54	1959	38	1943	16	75	Hepatolienography	D.C.
3	M	65	1960	40	1935	24	—	Hepatolienography	N.Y.
4	M	60	1963	44	1947	16	—	Hepatolienography	D.C.
5	M	71	1967	52	1948	19	—	Carotid arteriography	Ariz.
6	M	40	1968	20	1948	19	50	Hepatolienography	Ohio
7	M	52	1968	20	1936	32	—	Phlebography	N.Y.
8	M	57	1969	32	1944	24	45	Carotid arteriography	Calif.
9	F	54	1969	17	1932	37	50	Hepatolienography	Minn.
10	M	71	1970	43	1941	28	—	Carotid arteriography	Wash.
11	F	39	1970	22	1953	17	—	Hepatolienography	Mo.
12	M	54	1970	33	1949	20	24	Carotid arteriography	Calif.
13	M	53	1971	24	1942	28	75	Carotid arteriography	Pa.
14	F	44	1971	21	1948	23	30	Carotid arteriography	Pa.
15	M	65	1972	30	1937	34	20	Carotid arteriography	Minn.
16	M	50	1972	24	1946	25	—	Hepatolienography	Tex.
17	F	39	1972	20	1953	19	—	Carotid arteriography	Mich.
18	M	62	1972	37	1947	25	10–20	Femoral arteriography	N.Y.
19	M	48	1973	19	1945	28	—	Hepatolienography	Italy
20	M	60	1974	—	—	—	—	Femoral arteriography	Va.
21	M	32	1974	7	1949	25	78	Carotid arteriography	Pa.
22	F	53	1974	24	1945	29	15	Carotid arteriography	Pa.
23	M	53	1974	26	1948	26	48	Carotid arteriography	Mich.
24	M	73	1974	40	1942	32	24	Carotid arteriography	Canada
25	M	50	1975	24	1948	26	—	Carotid arteriography	Mass.
26	F	66	1975	26	1935	40	—	Carotid arteriography	Pa.

* From date of Thorotrast administration to date of death.

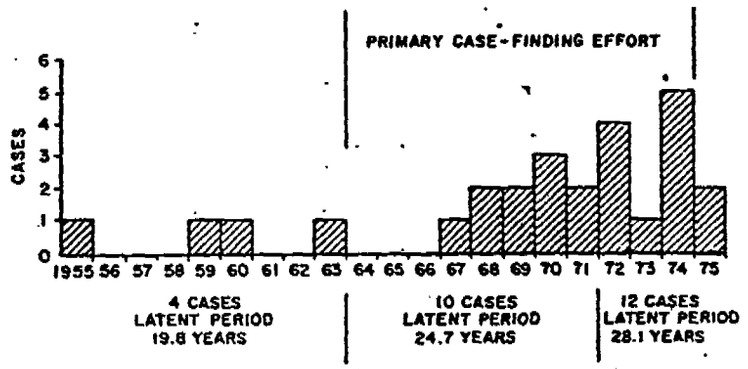

FIG. 1. Thorotrast-associated hepatic angiosarcoma cases, by year of death, United States, 1955–1975.

raphy for the earlier cases to lower dose carotid arteriography for the more recent cases. Taken together, these results suggest an increasing number of cases in the early 1970s occurring in recipients of relatively low-dose Thorotrast procedures who have had a more prolonged latent period.

Age at time of Thorotrast administration ranged from 7 to 52 years, with a mean of 28.5; 12 (48%) were between the ages of 20 and 29. Date of Thorotrast administration ranged from 1931 to 1953 with 17 cases (68%) having received Thorotrast in the 1940s. Age at death ranged from 32 to 73 with a mean of 54.5; 10 (38%) were between the ages of 50 and 54. If the above description of Thorostrast recipients (predominance of administration in the 1940s and in the third decade of life) is generally true for long-term survivors with retained Thorotrast, then it is possible that a sizable proportion would only now be going into their seventh decade and would continue to be at risk for the next decade or more.

Information on the precise dose administered is available for 14 cases, with a mean dose of 44.4 cc. Nine cases with carotid angiography had a mean dose of 39.9 cc and a median dose of 30 cc; 4 cases with hepatolienography had a mean dose of 61.8 cc; and 1 case with a femoral arteriogram had a dose of 10–20 cc.

Table 2 presents the underlying reason for Thorotrast administration in each case. Of particular interest are those cases where possible preexisting potentiating factors for hepatic fibrosis and malignancy exist. Of the 9 cases with hepatolienography, 4 (Cases Nos. 1,2,3, and 19) had somewhat obscure liver conditions [described as: (a) "toxic hepatitis" on liver biopsy, (b) cholecystitis with possible hepatic abscess and chronic hepatitis, (c) "paint poisoning," and (d) possible cholecystitis with jaundice] which could conceivably have related to subsequent liver disease. In addition, the 2 cases with hemolytic anemia who had hepatolienography (Cases 6 and 11) had histories of approximately 100 or more transfusions, suggesting a probable transfusional siderosis (O'Brien, 1977); this can independently lead to hepatic fibrosis and in these cases might have exacerbated the effects of Thorotrast.

One of the two cases with a femoral arteriogram (Case 18) had a prolonged history of diffuse art riovenous malformations of the lower extremities leading to

TABLE 2

INDICATION FOR THOROTRAST ADMINISTRATION IN CASES OF HEPATIC ANGIOSARCOMA

	No. of cases
Carotid arteriography	14
Auto accident-trauma	3
Seizure evaluation	3
Cerebrovascular accident	2
Diplopia	1
Proptosis	1
Hemiplegia	1
CNS syphilis	1
Recurrent "blackouts"	1
Organic mental syndrome	1
Hepatolienography	9
Hemolytic anemia–accessory spleen	2
Toxic hepatitis	1
"Paint poisoning"	1
Cholecystitis and jaundice	1
Cholecystitis and hepatic abscess	1
Postappendectomy abscess	1
Auto accident–abdominal injury	1
Ovarian tumor	1
Femoral arteriography	2
Leg injury in childhood	1
History since childhood of multiple A-V malformations with many operations	1
Phlebography	1
Industrial injury leading to subclavian vein thrombosis	1

multiple operations (at least one, but perhaps three, of which was preceded by Thorotrast studies). This patient also had a benign endovascular papillary hyperplasia of the hand (Clearkin and Enzinger, 1976) which remained dormant for approximately 20–30 years but which then grew rapidly 4 years prior to death and required four attempts at excision. This patient therefore had three separate unusual vascular diseases.

Interview data also yielded information on possible associated or potentiating factors. In addition to the two cases with probable transfusional siderosis mentioned above, two cases lived directly adjacent to two of the major iron-mining areas in the United States. Case 15 lived in Ironwood, Michigan, about one-quarter mile away from the mine for approximately 35 years; he worked as a machinist at the mine surface for approximately 10–15 years, and he would have been regularly exposed to the iron dust which was prevalent in the town. Case 9 lived in Chisholm and Gilbert, Minnesota, adjacent to a number of iron mines and taconite ore concentrations. It is uncertain, however, to what extent iron would have been inhaled or swallowed by these two cases, and whether this could have contributed to increased hepatic iron stores.

None of the cases had any history of occupational VC exposure, but two cases

had a definite history of occupational arsenical exposure. Case 5 was an insecticide sprayer and supervisor for approximately 30 years; an associate described his frequent use of arsenical rodenticides in later years and the probability that arsenicals were used on a wider scale in earlier years. Case 20 worked as a farm laborer during childhood and early adulthood in a farming area of Virginia where according to his brother they frequently sprayed arsenical insecticides on apple and peach trees.

Cases 7, 15, and 25 were machinists for either all or a major portion of their working years; it is uncertain, however, whether this might be a risk factor for this disease. There were, in addition, two cases (Nos. 4 and 25) generally considered chronic alcoholics by their associates, and four cases who had prolonged intake of barbiturate medications (Cases 13, 21 and 23, for epilepsy, and Case 4, who took them for approximately 8 years in conjunction with alcohol abuse).

There are, therefore, a substantial number of cases in this series in which additional risk factors could conceivably have potentiated the effects of Thorotrast. Moreover, in many cases retrieval of occupational, environmental, and historical data at this late date was not possible. [Case 1, e.g., with toxic hepatitis on liver biopsy at age 29, had rheumatic fever manifesting as chorea and nosebleeds as a child in Sweden in the early part of this century when the major textbooks of pediatrics recommended Fowler's solution, inorganic potassium arsenite, as the treatment of choice (Fruhwald, 1906); treatment records, however, are no longer available for this patient.]

A single case of acute lymphatic leukemia occurred in a 2-year-old child of Case 7, born approximately 20 years after the administration of Thorotrast. (Case 7 had developed a subclavian vein trombosis secondary to use of an air hammer. Phlebography and surgery at a local hospital were followed by phlebography and surgery at a university hospital; records are no longer available at either.)

DISCUSSION

Since the initial report of Thorotrast-induced HAS by MacMahon (1947) in the United States, much of the subsequent information concerning this relationship has come from centers in Europe and Japan. In the United States, Smoron and Battifora, in 1972, were able to identify 8 reported cases of Thorotrast-induced HAS; it is thought that a minimum of 4000–5000 patients received Thorotrast in this country (Thomas, 1951). Janower, in 1972, reported a retrospective cohort follow-up of 724 patients who had cerebal angiography with Thorotrast and did not find an increased incidence of liver tumors (Janower, 1972); the postulated reasons for this included the relatively small doses used and an insufficient latent period for the appearance of the long-term sequelae. Although other cohorts of Thorotrast recipients in this country were apparently identified in the past to be followed for the possible appearance of malignancy, no other large-scale reviews have been conducted in recent years (Telles, 1967). To appreciate fully the range of tumors seen in the United States secondary to Thorotrast administration a continuing cohort evaluation would be required; the current study deals only with the question of angiosarcoma.

A very important, and somewhat unexpected, finding of this study is the apparent increase in the number of cases of HAS in recent years. Part of this increase

may relate to the retrospective nature of the study in that 50% of the cases were identified by individual pathologists and recall may be greater for recent years; nevertheless, this increase appears to be larger than that seen so far for non-Thorotrast-related HAS, and it is difficult to see why there should be a selectiv overreporting of Thorotrast-induced HAS in recent years. At any given time the incidence rate for Thorotrast-induced HAS will depend on both the size of the dwindling population of Thorotrast recipients and the probably increasing rates of occurrence in long-term survivors whose accumulated radiation dose from retained Thorotrast is continually increasing. This study suggests that the point of peak occurrence in the United States may come later than the early 1970s and that physicians should be alerted to the possibility that cases will continue to occur for a decade or more.

It is clear from animal experiments that Thorotrast independently is carcinogenic (Roussy *et al.*, 1934; Selbie, 1936; Swarm *et al.*, 1962). As with other human carcinogens, however, not all recipients of a given dose of Thorotrast develop malignancy. In this study, in addition to reviewing the circumstances of Thorotrast administration for each case, we attempted to obtain data on the presence of additional risk factors for hepatic disease or angiosarcoma. Identified factors included preexisting hepatic or vascular disease and exposure to arsenic and iron. Arsenic has previously been shown to be related to both hepatic fibrosis (Morris *et al.*, 1974) and HAS (Regelson *et al.*, 1968; Lander *et al.*, 1975; Roth, 1957). Iron overload in hemochromatosis or transfusional siderosis can also lead to hepatic fibrosis (O'Brien, 1977), and there have been a few case reports of HAS in patients with hemochromatosis (Baker *et al.*, 1956; Kwittken and Tartow, 1968; Sussman *et al.*, 1974). To the extent that a Thorotrast recipient is exposed to additional risk factors this may increase the risk for development of HAS. It is also unclear why HAS predominates in some series of Thorotrast recipients (Horta *et al.*, 1974), cholangiocarcinoma in another (Mori *et al.*, 1973), and yet other studies have shown a fairly equal distribution between HAS, cholangiocarcinoma, and hepatocellular carcinoma (Faber, 1973; Van Kaick and Scheer, 1973). Again, the possible coexistence in a Thorotrast recipient of additional risk factors which promote the development of one of these tumor types may help determine the response of the liver to the administered Thorotrast. It would be very interesting to detail chemical exposure and medical histories within a cohort of Thorotrast recipients and to compare the findings for those who developed HAS with those who developed cholangiocarcinoma or hepatocellular carcinoma and with a control group of Thorotrast recipients who have not developed hepatic malignancies. By this means one could determine whether the multiple associations seen in some of our cases are a chance finding or of possible etiologic significance.

The male:female ratio of 19:7 is striking; even with removal from consideration of three cases where Thorotrast was administered for apparent military or occupational injury, the ratio still exceeds 2:1. In the series reported by Janower, 53% of Thorotrast recipients were male which suggests a fairly equal distribution by sex (Janower *et al.*, 1973); however, in the absence of knowledge concerning the bulk of Thorotrast recipients, this figure cannot be reliably accepted for the total population. Sex ratios have not always been listed in reviews of other Thorotrast cohorts, and it would be interesting to compile these data.

In the concluding discussion of the Third International Meeting on the Toxicity of Thorotrast held at Copenhagen in 1973, Rowland and others pointed out the importance of studying the children of Thorotrast recipients. The single case found in our study of acute lymphatic leukemia in the child of a Thorotrast recipient again raises this issue. Although this case could represent a chance occurrence, earlier reports have described the presence and effects of Thorotrast in the testes of recipients (Suckow *et al.*, 1961; Baserga *et al.* 1960), and testicular changes have been detailed under experimental conditions in rats (Tandon *et al.*, 1975). No epidemiologic evaluations have been performed on reproductive outcome for Thorotrast recipients or on illness in their offspring.

Thorotrast-associated cases constitute slightly more than 10% of the total number of HAS cases being reviewed in our study; VC-associated cases constitute a similar number. The remaining 75–80% of cases are currently under investigation.

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