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Evolution of Thorotrast-Induced Hepatic Angiosarcomas

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A histological review of 25 cases of thorotrast-induced angiosarcoma revealed characteristic antecedent or precursor changes which are similar to previously described changes present in hepatic angiosarcoma secondary to vinyl chloride, arsenicals, or of unknown etiology. The antecedent or precursor change consists of areas with simultaneous activation of both the hepatocytes and sinusoidal cells and associated lesions in the sinusoidal and perisinusoidal spaces. The hepatic cell plates surrounding these areas are compressed with subsequent development of fibrous septa at the interface between the areas of mixed hyperplasia and the areas of compression. In these multiple areas multicentric angiosarcomas develop in close approximation to the portal tracts but not to the thorotrast deposits.

INTRODUCTION

The purpose of this paper is to present the pathologic hepatic findings in 25 cases of angiosarcoma following the administration of thorotrast.[1] We have particularly evaluated early or antecedent (precursor) changes in the liver which are related to the subsequent development of angiosarcomas.

The carcinogenicity of thorotrast was demonstrated in animals by 1934 (Roussy *et al.*, 1934). Most of the tumors reported in these early experiments were spindle-cell sarcomas (Selbie, 1936), but osteosarcomas and other tumors were subsequently reported (Guimaraes *et al.*, 1955; 1956). The first thorotrast-induced neoplasm in man, an angiosarcoma, was reported by MacMahon and co-workers (MacMahon *et al.*, 1947); the tumor had occurred in a patient who had received thorotrast for angiographic study of the liver 12 years before.

Thorotrast was introduced for radiographic use as a contrast medium in man in Germany in 1928. Because of its high atomic weight, relative chemical inertness, and other desirable properties, thorotrast gained great favor among radiographers for angiographic procedures. Despite the early report by MacMahon, its use continued in many regions of the world until the early 1960s. An ever increasing number of reports of its radiation-associated hazards (Baserga *et al.*, 1960; Battif-

[1] Thorotrast (a proprietary colloidal thorium dioxide preparation) was first manufactured by the Heyden Chemical Company and used in Germany in 1928. In 1954 the Fellows–Testagar Company of Detroit, Mich. began to produce and sell Thorotrast worldwide. Although the trade name "Thorotrast" has been used by at least two firms, most of the literature uses "thorotrast" in a generic sense to describe a 25% colloidal suspension of thorium dioxide, stabilized by hydrolyzed dextrin. The word "thorotrast" is used in its generic sense in this paper.

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ora, 1976; Looney, 1960) including several types of malignant tumors in various organs, brought about discontinuance of thorotrast as a contrast medium. However, this did not occur until after literally tens of thousands of patients had received intravascular injections of thorotrast worldwide.

Angiosarcoma of the liver is relatively rare (Edmondson, 1958). It has been associated with long-term exposure to arsenicals and copper compounds, as well as thorotrast (Pimentel and Menezes, 1977; Regelson *et al.*, 1968). More recently angiosarcomas have been reported in workers exposed to vinyl chloride during its polymerization to polyvinyl chloride (Creech and Johnson, 1974; IAEA Report No. 106, 1965).

The gross and histological features of hepatic angiosarcomas induced by thorotrast have been well described (Edmondson, 1958; Ishak, 1976; MacMahon *et al.*, 1947; da Silva Horta 1956; 1967). Typically angiosarcoma develops with the formation of large peliotic blood lakes or cavernous spaces lined by sarcoma cells, of hepatic cellular necrosis, and of fibrosis. Late features include distortion of the hepatic architecture associated with thorotrast deposition as well as hemorrhagic necrosis.

Our evaluation of the changes in livers with thorotrast-induced angiosarcomas is part of a larger epidemiologic and pathologic study of approximately 240 cases of hepatic angiosarcomas which is in progress. This series includes angiosarcomas from persons exposed to vinyl chloride, arsenic, a variety of suspected carcinogens including pesticides, as well as cases without known etiology. There appears to be considerable similarity in the histological development and features of the angiosarcomas caused by these various etiologic factors.

The epidemiological features of the thorotrast cases are being presented at this meeting as a separate report (Falk *et al.*, 1979).

MATERIALS AND METHODS

The material consisted of sections of the livers from 25 patients with thorotrast-induced hepatic angiosarcomas. All were part of a national survey conducted by epidemiologists at the Center for Disease Control to study the potential relati nship of hepatic angiosarcoma to occupational and environmental factors. Eight cases were from the files of the Armed Forces Institute of Pathology. The slides of most of the cases have been filed in the Laboratory of Pathology, National Cancer Institute. In some instances, sections from both surgical biopsies as well as autopsy material were available for study.

For comparison (but not included as part of the present report) we also reviewed sections of the liver from three Japanese patients who had received thorotrast and from two patients in the series of cases collected by Professor da Silva Horta. Two of the Japanese cases did not have hepatic angiosarcoma but had antecedent changes in the liver.

Ten surgical biopsy specimens of the liver were available from eight patients. In another case slides from both the surgical biopsy and autopsy were reviewed. In 16 cases slides from autopsy only were studied. In addition to hematoxylin and e sin-stained sections, some cases were studied with special stains including connective tissue stains such as the Masson trichrome and chromotrope aniline blue, silver impregnations, and iron reactions as well as periodic acid–Schiff (PAS reaction) following glycogen digestion with diastase.

RESULTS

The earliest age at which thorotrast was injected was 7 years and this patient died at 32 years of age after an interval of 25 years (Table 1). Most of the patients had thorotrast injections during the third and fourth decades of life. The average age at death was 55 years, with the age at injection ranging from 7 to 52 years. The average interval between injection and death was 25 years. These data are in general agreement with data reported by others (Marsteller *et al.*, 1973; da Silva Horta, 1956). Further discussion of the data associated with the dose of thorotrast, age, sex, and other epidemiological factors will be presented in the paper by Falk *et al.*

Information about the distribution of angiosarcoma in organs other than the liver was available for 20 of the 25 cases (Table 2) with hepatic angiosarcoma. Eight of the 20 had metastases. Six of the eight had pulmonary or pleural metas-

TABLE 1
25 CASES OF THOROTRAST-INDUCED HEPATIC ANGIOSARCOMA

Case	Accession no.	Sex	Year thorotrast injected	Amount thorotrast injected (ml)	Age at injection (years)	Age at death (years)	Interval between injection and death (years)
	A74-320	F	1953	N.A.[a]	22	39	17
1	S74-3015						
2	S74-3008	F	1932	50	17	54	37
3	S74-2323	M	1942	75	24	53	28
4	A74-223	M	1949	24	33	54	20
5	A75-33	M	1937	20	30	65	34
6	A74-226	F	1945	15	24	53	29
7	S75-2410	M	1948	N.A.	24	50	26
8	S75-389	M	1941	N.A.	43	71	28
9	A74-279	M	1948	50	20	40	19
10	A55-75	F	1931	72	29	52	23
11	A76-2	M	1944	45	32	57	24
	S76-75						
12	A77-32	F	1953	N.A.	20	39	19
13	A77-18	M	1946	N.A.	24	50	25
14	A77-28	M	N.A.	N.A.	N.A.	60	N.A.
15	A77-65	M	1936	N.A.	20	52	32
16	A77-31	F	1948	30	21	44	23
17	[b]	M	1948	48	26	53	26
18		M	1949	78	7	32	25
19		M	1947	10–20	37	62	25
20		M	1943	75	38	54	16
21		M	1947	N.A.	44	60	16
22		M	1948	N.A.	52	71	19
23		M	1942	24	40	73	32
24		F	1935	N.A.	26	66	40
25		M	1935	N.A.	40	65	24

[a] Information not available.

[b] Cases 17 to 24 from AFIP files. Case 25 referred to Dr. Popper but not accessioned in Laboratory of Pathology, NCI.

TABLE 2
HEPATIC ANGIOSARCOMA CASES WITH ANGIOSARCOMA IN OTHER ORGANS

Case no.	Lung/pleura	Kidney	Adrenal	Bone	Spleen	Other organs
1	X					
4	X	X	X	X		
6		X	X	X	X	
9	X					
10				X	X	Diaphragm
11	X					Brain, peritoneum
14	X		X			Skin, heart
25	X		X			Lymph nodes

tases, four had adrenal gland and three had bone metastases. Other organs were occasionally involved by angiosarcoma as shown in Table 2.

The average weight of the livers was 2673 g, and the range was from 675 to 4755 g (Table 3). As expected most of the spleen weights were below 100 g (median weight, 80 g) because of fibrosis and atrophy of the red and white pulp due to

TABLE 3
LIVER AND SPLEEN WEIGHTS

Case	Liver weight (g)	Spleen weight (g)
1	2670	N.A.[a]
2	N.A.	N.A.
3	N.A.	N.A.
4	1500	400
5	3445	55
6	1640	40
7	N.A.	N.A.
8	N.A.	N.A.
9	3700	N.A.
10	3650	115
11	3400	60
12	1600	10
13	675	33
14	4000	N.A.
15	2090	30
16	1800	17
17	2450	80
18	2750	150
19	N.A.	N.A.
20	4755	228
21	2660	150
22	2650	150
23	N.A.	N.A.
24	N.A.	N.A.
25	2250	100

[a] Information not available.

deposits of thorotrast. The average weight of the spleens was 108 g; the range was from 10 to 400 g.

Antecedent (Precursor) Changes Preceding Angiosarcoma

A characteristic finding was the activation and increase in the number of sinusoidal lining cells, with or without sinusoidal dilatation and associated with hyperplasia of the hepatocytes. This activation was noted within focal, poorly circumscribed areas of the liver lobule. There was no consistent topographical distribution of these areas, although frequently they were at the periphery of the lobules, often in close proximity to the portal tracts.

The activated sinusoidal lining cells showed prominent cytoplasm that gave a positive PAS stain, not influenced by diastase digestion. Often, the sinusoids lined by these cells were focally dilated and the perisinusoidal space of Disse was widened. Consistently, the hepatocytes in these areas were hyperplastic and had abundant pale-staining cytoplasm and often multiple nuclei. They were intermixed with small hepatocytes with increased nucleocytoplasmic ratio. The hepatocytes also appeared hyperthrophied and the hepatic cell plates were more than one cell thick.

These areas of sinusoidal cell proliferations and hepatic cell hyperplasia and hypertrophy produced irregular enlargement and distortion of hepatic lobules (Fig. 1). The parenchyma appeared compressed around these nodular areas and

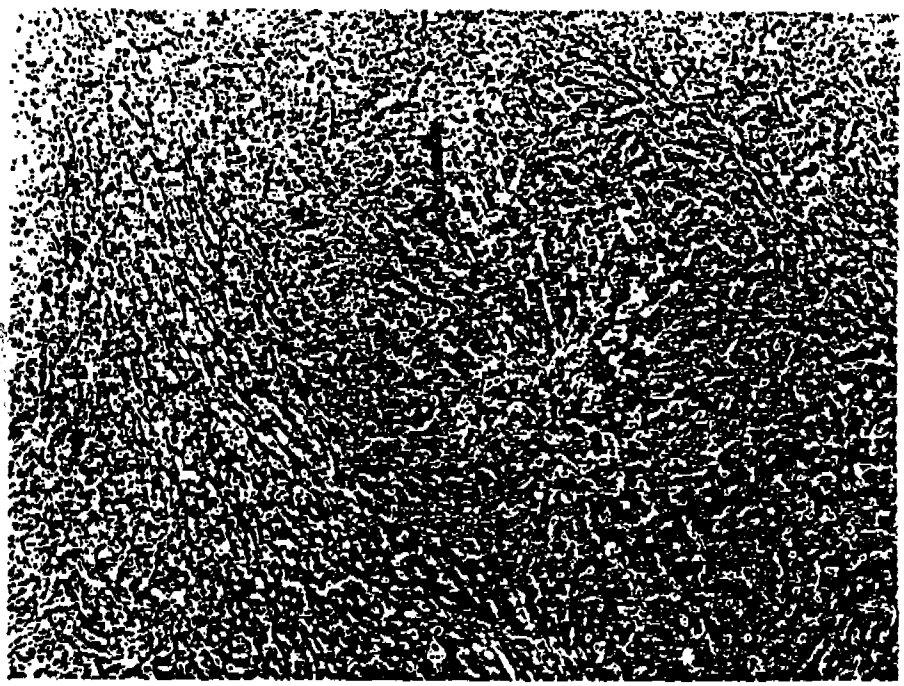

FIG. 1. Case 20. Areas of hyperplasia and hypertrophy of both hepatocytes and sinusoidal cells seemingly exerting pressure on the surrounding parenchyma with compression atrophy. Note also accentuation of hypertrophy in the center of the area (arrow). Deposits of thorotrast are present in the surrounding area of compression. H&E. ×40.

the hepatocytes in these compressed areas exhibited atrophy, degeneration, and occasionally necrosis (Fig. 2). Moreover there were increased numbers of inflammatory cells, variable congestion, hemorrhage, and focal fibrosis. Macrophages contained cellular debris and some hemosiderin. A few of the macrophages in the compressed areas had thorotrast granules (Fig. 3). By contrast thorotrast granules were rarely found in macrophages within the hyperplastic areas. The hepatocytes in the compressed areas also showed decreased amounts of lipofuscin in contrast to prominent amounts of lipofuscin in areas of hyperplasia. On the border between the areas of hyperplasia and compression bile canaliculi often were dilated and had multiple, small diverticuli which were most easily seen in silver-impregnated sections (Fig. 4).

Also, the distribution of reticulin and collagen fibers differed in the areas of hyperplasia as compared to the areas of compression. In the latter, loss of hepatocytes with subsequent collapse resulted in thin fibrous septa, some extending to portal tracts but more often randomly located within the hepatic lobules. These thin fibrous bands sometimes joined larger areas of dense fibrosis involving portal tracts with heavy deposits of thorotrast. The overall appearance was similar to but m re irregular than that of cirrhosis.

Transition to Angiosarcoma

Two patterns were observed, both of which could occur in the same liver. One pattern of transition was the proliferation of atypical sinusoidal cells without the

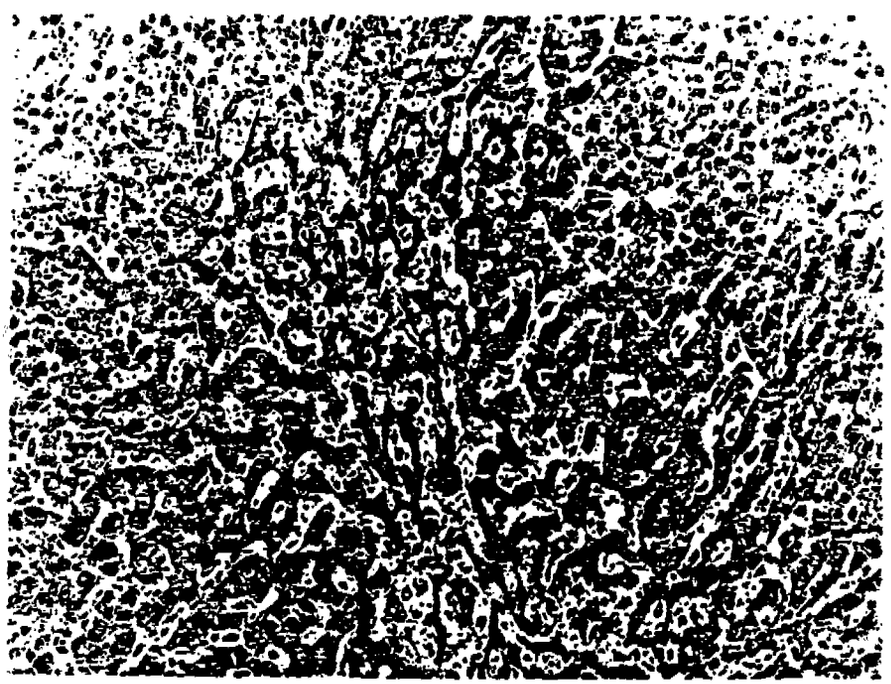

FIG. 2. Case 20. Two areas of combined hepatocytic and sinusoidal cell hyperplasia compressing intervening parenchyma. In the hyperplastic areas the hepatic plates are more than one cell thick as indicated by the position of their nuclei near the sinuses. Note also polymorphism of the sinusoidal cells. H&E, ×100.

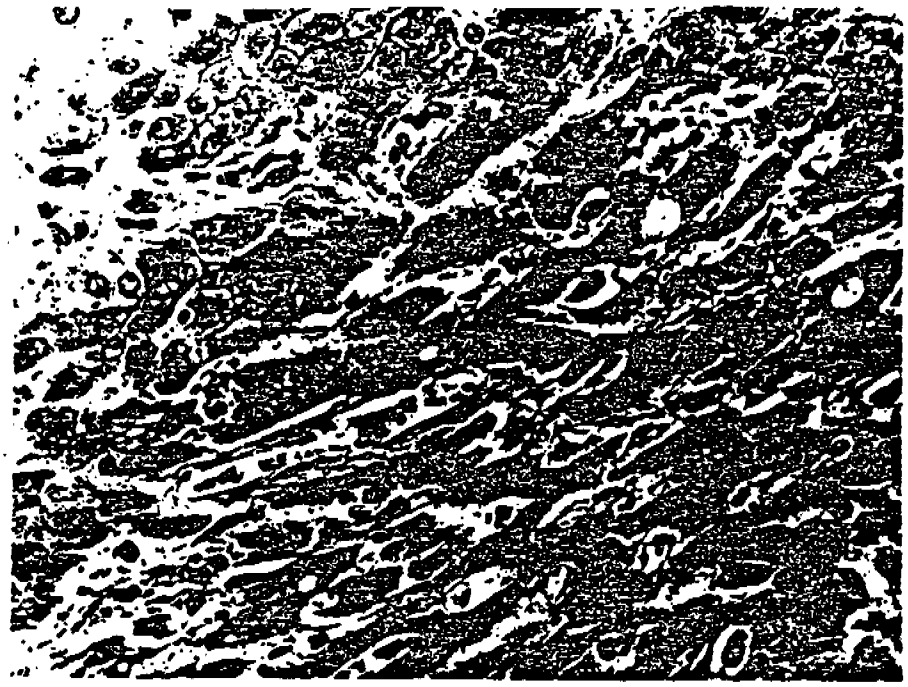

FIG. 3. Case 20. Border of hyperplastic and compressed areas. Note dilated bile canaliculi and binucleated hepatocytes with nuclear hyperchromatism in the hyperplastic area. In the compressed area there are more macrophages, and some of them containing thorotrast are arranged in clusters. H&E, ×50.

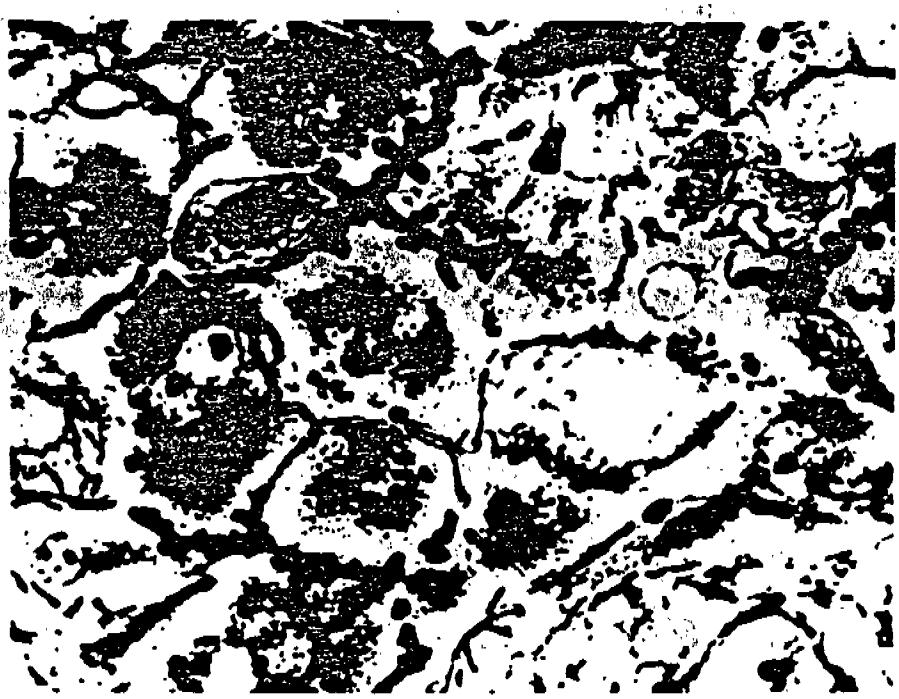

FIG. 4. Case 20. Border of hyperplastic area. Lipofuscin granules surround dilated bile canaliculi which contain ramified bile plugs. Note prominent diverticuli along bile canaliculi and the slight increase of the reticulum framework. Silver impregnation, ×400.

dilatation of sinusoids (Fig. 5). Most often this pattern of angiosarcoma developed in the periphery of the lobules adjacent to portal tracts and was associated with increased numbers of lymphoid and histiocytic inflammatory cells. Frequently, microscopic or small blood lakes lined by angiosarcoma cells were formed. A second pattern consisted of conspicuous sinusoidal dilatation associated with perisinusoidal fibrosis in the space of Disse (Fig. 6). The proliferated cells lining the sinusoidal spaces exhibited variable degrees of atypia and had large, hyperchromatic nuclei (Fig. 7). The widened space of Disse also contained increased numbers of lipocytes, or Ito cells, macrophages and fibroblasts, together with a few inflammatory cells. Thus, there was a spectrum of changes starting in the areas of intralobular hyperplasia with a proliferation of sinusoidal lining cells, followed by increasing degrees of sinusoidal cell atypia and anaplasia eventuating in multifocal angiosarcoma (Fig. 8).

Both patterns of proliferation and transition were found adjacent to portal tracts and sometimes even the small angiosarcomas extended into the portal tracts (Fig. 9). Dense portal-tract fibrosis and large fibrotic areas extending from portal tracts were associated with the heavier deposits of thorotrast. In these denser portal tracts bile ductular proliferation was rare. This is in contrast to the changes observed in the livers of vinyl chloride workers in which bile ductular proliferation is very prominent. Also, the fibrosis in the thorotrast cases was more coarse and irregular than that observed in the cases associated with vinyl chloride.

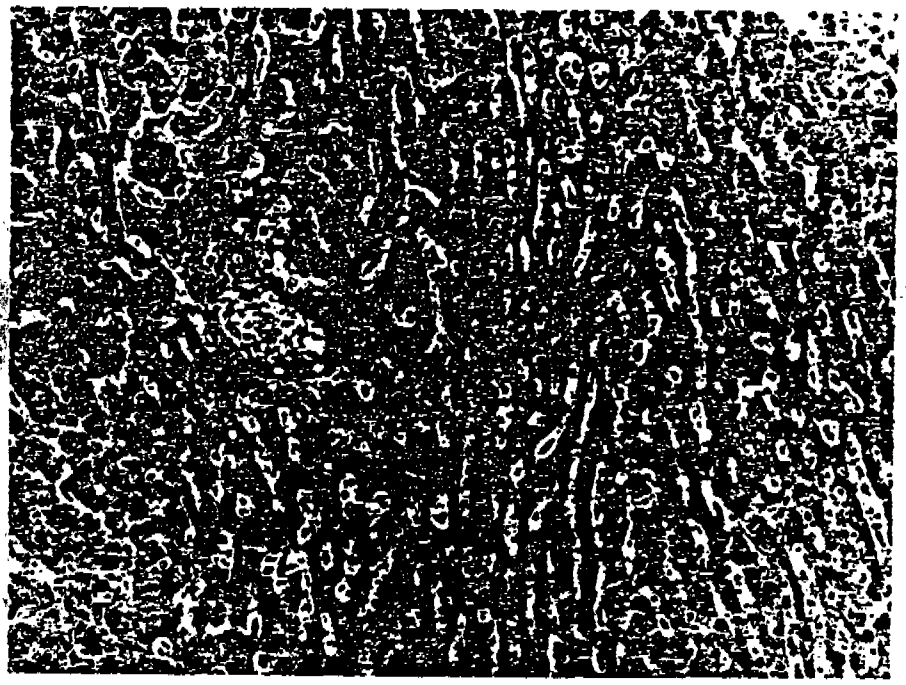

FIG. 5. Case 20. Accentuated hyperplasia and hypertrophy of the hepatocytes in the center of the photomicrograph. Slightly dilated sinusoids are lined by proliferated sinusoidal cells. H&E, ×100.

Evolution to Fully Developed Angiosarcomas

The developing angiosarcomas appeared to be confined to the areas of hyperplastic parenchyma containing the "activated" sinusoidal lining cells (Fig. 5, 7, 8). As the peliotic and sinusoidal spaces lined by angiosarcoma cells enlarged, irregular spurs of fibrotic hepatic cords projected into the blood-filled spaces. These papillary projections were covered by a single or multiple layer of angiosarcoma cells. The latter were either irregular, polyhedral, and atypical cells with a tendency to become detached, or they were tectorial and retained a spindle shape as they lined the vascular spaces and enveloped the papillary projections. Further enlargement resulted in grossly visible peliotic lakes which sometimes were partially lined by angiosarcoma cells. Hepatic parenchyma between the gross nodules of angiosarcoma cells which did not line hepatic sinusoids or form vascular spaces were also seen. The angiosarcoma cells in these solid nodules were either elongated and spindle shaped or were large and fusiform. Cellular anaplasia in these solid areas was often so pronounced that it was difficult to identify the tumor as an angiosarcoma.

Often all of these patterns were seen in various sections of the same liver which was diffusely involved with angiosarcoma.

Other Hepatic Changes

As previously noted hemorrhage was commonly associated with the angiosarcomas, but there was remarkedly little stainable iron within the angiosarcomas.

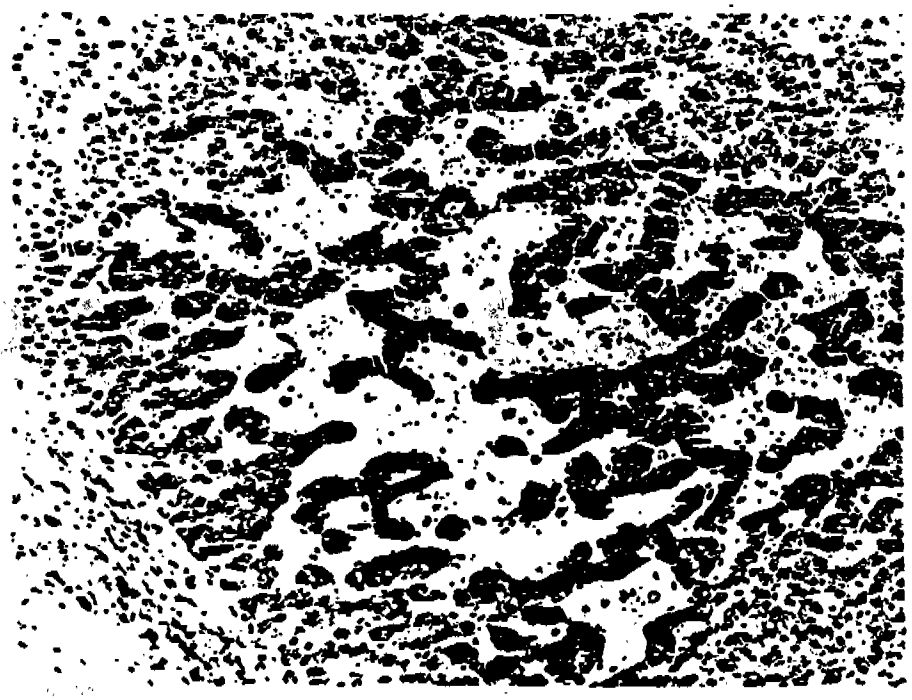

FIG. 6. Case 1. A focal circumscribed area of sinusoidal dilatation without conspicuous compression of hepatocytic plates. This area is adjacent to a portal tract. H&E. ×100.

Extramedullary hematopoiesis was recognizable in 24 of the 25 cases. This varied from occasional hematopoietic foci to extensive involvement of nearly every sinusoidal space. No relationship to the extent of tumor development or fibrosis of the spleen or liver could be established. There were too few specimens of bone marrow to permit correlation of bone marrow changes with extramedullary hematopoiesis in the liver. In one case extramedullary hematopoiesis was noted in the spleen with no evidence of hematopoiesis in the liver.

DISCUSSION

Hepatic angiosarcoma in the human is a rare tumor with fewer than 200 cases reported in the world literature. A significant fraction of these reported cases have been associated with thorotrast injections. Due to its rarity there are relatively few accounts of the characteristics of this tumor, particularly with respect to its initiation and evolution. The histological observations on the fully developed lesions in the 25 cases reported in this paper are similar in most respects with the descriptions previously reported by others. The reports by da Silva Horta *et al.* (1956, 1967) based on studies of material obtained from long-term epidemiological studies of persons injected with thorotrast have provided the most comprehensive histological descriptions, particularly of the final stages of this disease. These reports emphasized the importance of lymphatic obstruction with fibrosis as one

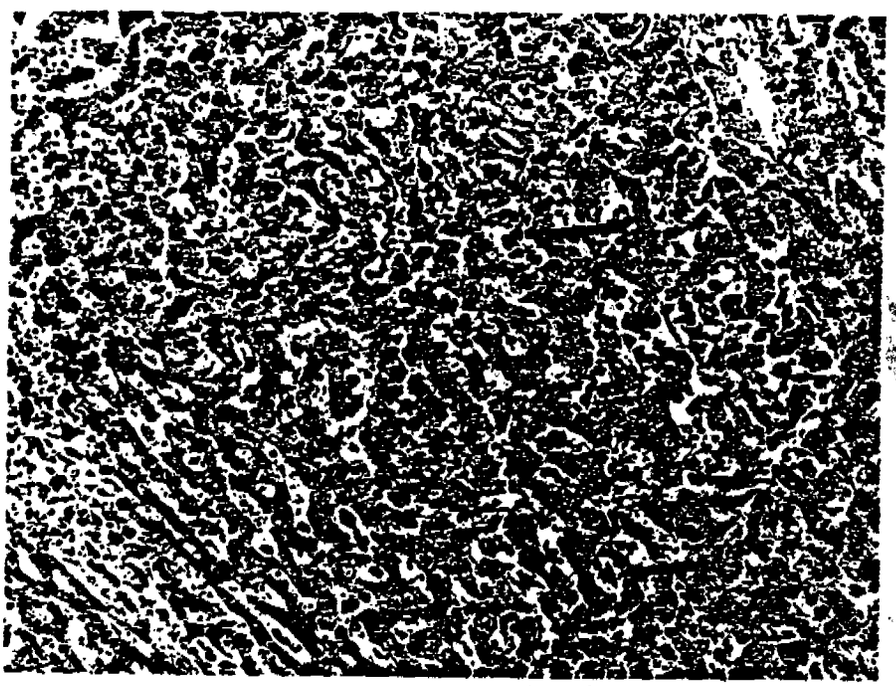

FIG. 7. Case 1. Proliferation of sinusoidal cells within a hyperplastic area. The sinusoidal cells consist of a variety of mesenchymal cells. The angiosarcoma cells have bizarre nuclei and occasionally are piled up on the sinusoids (arrows). The parenchyma around the hyperplastic area shows atrophy, accumulation of macrophages, and thorotrast deposits. H&E, ×125.

FIG. 8. Case 1. Nodular accumulation of angiosarcoma cells within mixed hyperplastic area. Note extensive thorotrast deposition in the surrounding compressed area. H&E, ×100.

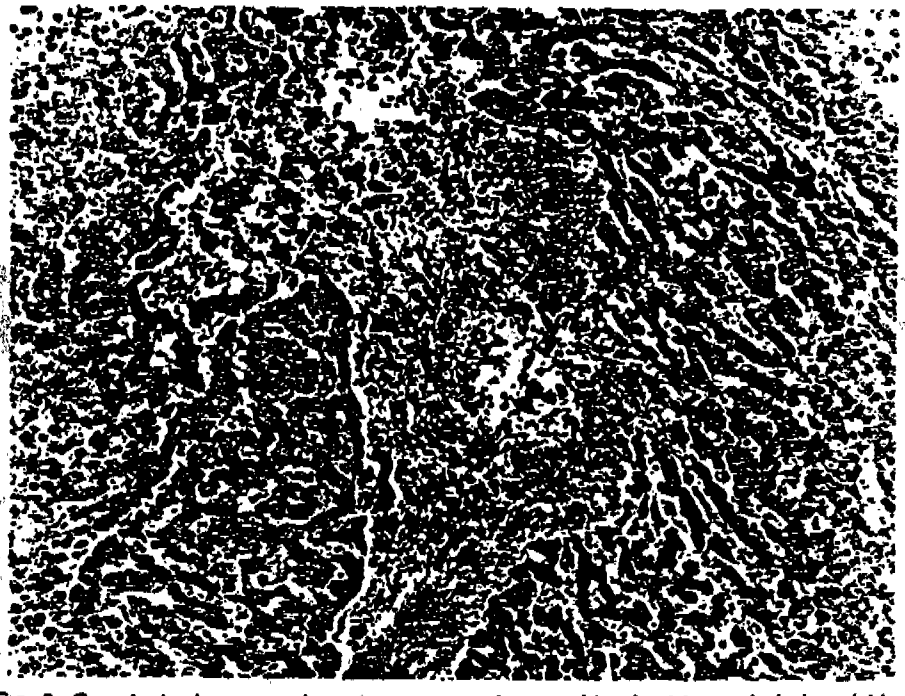

FIG. 9. Case 1. Angiosarcoma in and near a portal tract with mixed hyperplasia in neighboring parenchyma. Note hepatocytes in two-cell thick plates. H&E, ×100.

of the prominent factors leading to gross scarring of the liver. In our study the emphasis has been on the earliest lesions and their development to angiosarcomas which has so far not been fully described.

The distribution of thorotrast shortly after injection has been described by Tessmer and Chang (1967). These investigators showed a progressive redistribution of thorotrast within the rat liver as a function of time, but there was only occasional focal reticuloendothelial cell damage observed in areas of the liver lobule corresponding with the early distributions of thorotrast.

The presumptive carcinogenic factor for hepatic angiosarcomas due to thorotrast is the α radiation emitted by the thorium. Chemical toxicity cannot be excluded although it appears unlikely from experimental data (Bensted, 1967). However, the multicentric foci of angiosarcoma do not arise in topographical association with the heaviest deposits of thorotrast but rather develop in areas of mixed hyperplasia and hypertophy of hepatocytes and sinusoidal cells where there is little thorotrast deposition. This focal development of angiosarcomas suggests a complex carcinogenic effect of the α particles, which may have been initiated early after injection when thorotrast was more diffusely distributed in the liver. All of this focuses interest on the antecedent, precursor changes.

It was previously reported (Creech and Johnson, 1974, Marsteller *et al.*, 1973; Thomas *et al.*, 1975) that the development of hepatic angiosarcomas in workers engaged in the polymerization of vinyl chloride was preceded or accompanied by the development of a peculiar hepatic fibrosis. The latter consisted of focal subcapsular fibrosis which was grossly visible at surgery. In addition there were areas of intralobular, perisinusoidal fibrosis which were topographically related to proliferation and activation of sinusoidal lining cells and cells in the space of Disse. These changes were associated with focal hypertrophy and hyperplasia of hepatocytes (Popper *et al.*, 1977). The same changes have also been observed in the cases of thorotrast-induced hepatic angiosarcomas reported in this paper. Also, we have observed these same changes in cases of hepatic angiosarcomas associated with arsenical exposure as well as "idiopathic" cases with no known etiology.

Involvement of other organs by angiosarcoma, presumably metastases, occurred in some of the cases included in this report, which raises the question about whether the hepatic lesions are primary. The quantitative predominance of the hepatic involvement suggests that the liver was the primary site though in at least one reported case of unknown etiology (Ludwig and Hoffman, 1975) the relationship may have been reversed. The further question can be raised whether the multicentric foci in the liver represent metastases from a single primary hepatic lesion. However, the observation of multicentric angiosarcomas developing in antecedent, precursor lesions is considered to be strong evidence for primary multicentric origin in the liver (Fig. 10).

Extramedullary hematopoiesis has been reported in association with angiosarcomas due to multiple etiologies (Ishak, 1976). This feature is a nearly constant finding in thorotrast-induced angiosarcomas, while comparatively rare in livers with angiosarcomas due to other causes. The hematopoietic foci were found exclusively in sinusoidal spaces or in cavernous blood-filled spaces.

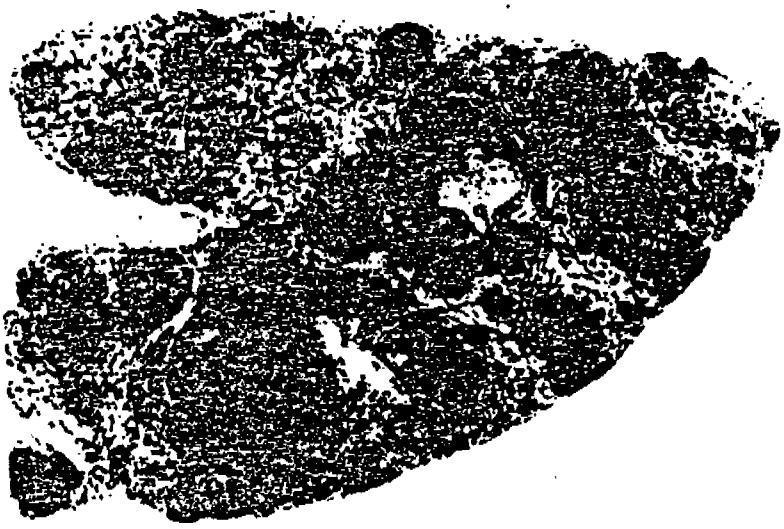

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FIG. 10. Case 10. Cut surface of 3650-g liver showing multicentric angiosarcoma. The dark, hemorrhagic angiosarcoma nodules are interspersed with pale areas of necrosis and fibrosis.

Unlike the large spleens found in vinyl chloride workers which weighed up to 1000 g, the spleen in thorotrast cases were markedly shrunken and fibrotic as a result of the effect of radiation. Only one of the cases in this series showed metastasis to the spleen. The infrequent spleen metastasis from a primary hepatic angi sarcoma, as well as the rarity of primary angiosarcoma development in the spleen has previously been noted (IAEA Report No. 106, 1965) and it has been suggested that this may be the result of the extensive fibrotic changes occurring in the spleen which would mitigate against radiation-induced tumors.

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