Original Contributions

Hepatic Disease Among Workers at a Vinyl Chloride Polymerization Plant

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• **Eleven cases of hepatic disease, including seven cases of hepatic angiosarcoma, have been identified to date among men employed at one vinyl chloride polymerization plant. The earliest diagnosis was made in April 1964. The two most recent cases, both angiosarcoma, were diagnosed in February 1974 as a result of systematic medical screening for liver abnormalities among workers at the plant. Ages at diagnosis have ranged from 36 to 58 years for the seven patients with angiosarcoma and from 28 to 56 years for the four patients with nonmalignant disease; durations of employment before diagnosis have ranged from 12 to 28 years and from 5 to 29 years. All 11 persons had worked in close and continuous contact with various phases of the vinyl chloride polymerization process. Review of pathologic material suggests the presence in both tumor and nontumor cases of portal fibrosis and atypical sinusoidal lining cells. A direct causal relationship between exposure to vinyl chloride monomer and pathologic findings is postulated.**

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CREECH and Johnson[1] recently reported the occurrence of three cases of angiosarcoma of the liver among workers at a polyvinyl chloride (PVC) production plant in Louisville. Because this tumor is extraordinarily rare (only about 25 cases are estimated to occur each year in the entire United States), the existence of such cases in this particular setting strongly suggests a causal relationship to some phase of the PVC production process. Recent animal studies being conducted in Italy support the concept that exposure to vinyl chloride monomer (VCM) may be the mechanism involved (C. Maltoni et al, unpublished data).

See also p 64.

Beginning in late January 1974, intensive efforts have been devoted to clinical and epidemiologic studies of past and present workers at the Louisville plant, as well as at other PVC production plants elsewhere, in order to define more precisely the extent of health risks among vinyl chloride workers. This report summarizes findings to date with respect to both malignant and nonmalignant hepatic disease among workers at the Louisville plant, particular emphasis being given to epidemiologic features.

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BACKGROUND

The production of PVC by polymerization of VCM began in Germany about 40 years ago, with production in the United States starting about five years later. The industry grew rapidly after World War II, and growth has continued in recent years at a rate of about 14% per year. Currently in the United States, 14 plants employing about 1,500 workers produce VCM, while 37 plants employing about 5,000 workers polymerize PVC from VCM. Current annual production of PVC in the United States is estimated at approximately 4.4 billion pounds, or 25% of world production.

The B. F. Goodrich PVC polymerization plant in Louisville first began operations in 1942. The number of persons employed at the plant directly in PVC polymerization has steadily increased, reaching a fairly stable level of 250 to 300 workers by the late 1950s. At present, in addition to 271 persons engaged directly in PVC polymerization, about 850 persons are employed at the plant in other activities such as synthetic rubber production, compounding and milling operations, managerial and clerical positions, and maintenance work outside PVC polymerization areas.

Until 1966, VCM as well as PVC was produced at the Louisville plant. Since that time, however, all VCM used at the plant has been shipped by tank car from other facilities. The VCM is unloaded, stored, and then piped into large polymerization reactor vats through an essentially closed system. Each reactor receives a measured amount of VCM as well as appropriate catalysts, stabilizers, emulsifiers, and additives (and other monomeric compounds if copolymers or terpolymers are being produced), and the reaction is carried to the desired end point. Polymerized material is dropped into secondary tanks from which unreacted VCM is recovered and recycled through a closed system; it then enters tertiary tanks from which it is concentrated, dried, and packaged. The end product consists of three different materials: (1) PVC resin (a powder with the texture of refined sugar), (2) PVC paste (a very fine powder with the texture of processed flour), and (3) PVC latex (a stable suspension of PVC in liquid).

For workers in PVC polymerization, the point of greatest probable exposure to VCM occurs after poly-

merization, when reactors are opened and cleaned. Although the air within reactors is replaced several times before opening, a short burst of VCM may be released from reactors immediately on opening. In addition, some PVC remains encrusted within reactors which, because of its porous structure, may retain significant amounts of entrapped VCM. In the process of chipping and cleaning this material from within reactors, retained VCM is released. Until the late 1960s, this cleaning process was done manually by a man lowered into the reactor for that purpose. Since that time, high-pressure water hoses have been introduced for cleaning reactors, and manual cleaning is done much less frequently. This change in work practice was designed primarily to prevent acro-osteolysis, a disease peculiar to PVC workers and characterized by Reynaud phenomenon, sclerodermalike changes of the hands, and lytic lesions in the distal phalanges.[2,3]

CLINICAL AND PATHOLOGIC FINDINGS

Table 1 summarizes salient features for each case of hepatic angiosarcoma and nonmalignant liver disease diagnosed to date. Review of death records for plant employees disclosed a total of five cases of angiosarcoma of the liver diagnosed in PVC workers over the ten-year period between 1964 and 1973 (cases 1 through 5). No cases were found diagnosed before 1964, and no cases were found of hepatic carcinoma or of angiosarcoma primary at other sites. A further review of medical histories of PVC workers employed at the plant disclosed four additional men with a known history of nonmalignant liver disease demonstrated by tissue biopsy and diagnosed between 1968 and 1973 (cases 8 through 11).

Because of concern aroused by the discovery of hepatic angiosarcoma in workers, a medical screening program aimed at detecting hepatic abnormalities was instituted at the Louisville plant. All current employees, whether engaged in PVC polymerization work or not, were examined (see p 64). As a result of this program, two additional cases of angiosarcoma of the liver were diagnosed, both in PVC workers (cases 6 and 7). At the present time, no cases of angiosarcoma of the liver or of nonalcoholic liver disease as demonstrated by biopsy have yet been identified among non-PVC employees at the plant. All patients have been white men.

Table 1.—Clinical

Case No.	Age at Diagnosis/ Race/Sex	Month and Year of Diagnosis	Month and Year of Death	Initial Symptoms
Hepatic Tumors				
1	52/W/M	4/64	4/64	8/63-Fatigue 1/64-Right upper quadrant pain
2	43/W/M	8/67	1/68	9/66-Fatigue, "pleurisy" 8/67-Epigastric "knot" and pain
3	36/W/M	5/70	9/71	1/70 and 5/70-Melena
4	49/W/M	3/73	3/73	12/63 and 5/65-Melena and hematemesis
5	58/W/M	12/73	12/73	7/73-Weakness and weight loss
6	45/W/M	2/74	...	8/73-Fatigue, "pleurisy"
7	43/W/M	2/74	...	Asymptomatic
Nonmalignant Hepatic Disease				
8	46/W/M	12/68	...	10/68 and 11/68-Melena
9	28/W/M	1/72	...	9/71-Chest pain, weight loss
10	56/W/M	9/73	...	2/73-Hospitalized for hernia repair, icterus noted
11	56/W/M	9/73	...	9/73-Hospitalized for cholelithiasis

Cases of Hepatic Angiosarcoma

Ages at diagnosis for the seven patients with tumors (cases 1 through 7) have ranged from 36 to 58 years (average age, 46.7). Initial clinical features have varied widely; there were no signs or symptoms in case 7. Four patients (cases 1, 2, 5, and 6) were first seen with weakness and tiredness; two of these also had intermittent pleuritic pain. These symptoms by themselves were not sufficiently severe to warrant medical evaluation until the appearance of acute abdominal pain, pronounced weight loss, or abnormal findings on serologic screening. Two patients (cases 3 and 4) were entirely asymptomatic until the abrupt onset of gastrointestinal bleeding. Two patients had clinically obvious hepatosplenomegaly (cases 2 and 5), but four (cases 3, 4, 6, and 7) had normal physical findings. While all seven patients had evidence of liver function abnormality at time of initial work-up, no consistent pattern emerged, and in several instances abnormalities were only slight (cases 2, 3, 4, 6, and 7). In several cases, relatively mild hepatic dysfunction coexisted with either far-advanced portal hypertension (cases 3 and 4), unresectable angiosarcoma

and Pathologic Findings of Cases of Liver Disease

Physical Findings	Hepatic Work-up*	Pathologic Findings†
1/64-Right upper quadrant tenderness	1/64-Moderate elevation in TB, SGOT	1/64-OLB: slight focal hepatitis 3/64-NLB: unchanged 4/64-PM: hepatic angiosarcoma with metastases
8/67-Epigastric mass and splenomegaly	8/67-Mild elevation in AP, SGOT, LDH Platelet count, 33,000/cu mm Liver scan: large defect, splenomegaly	8/67-OLB: angiosarcoma 1/68-PM: hepatic angiosarcoma with spread to diaphragm and abdominal wall
1/70-No abnormalities 5/70-Hepatosplenomegaly	5/70-Mild elevation in TB, AP, SGOT, LDH Liver scan: large defect Esophogram: varices	5/70-OLB: angiosarcoma No PM
12/63-No abnormalities 5/65-Splenomegaly	5/65-Elevated SGOT Esophagoscopy: varices	5/70-OLB: toxic hepatitis 10/70-NLB: hepatitis, cirrhosis 10/70-OLB: slight hepatitis 3/73-PM: hepatic angiosarcoma
7/73-Hepatosplenomegaly	7/73-Marked elevation in AP Mild elevation in TB, SGOT Liver scan: diffuse disease, hepatosplenomegaly	7/73-NLB: fibrosis OLB: periportal inflammation and fibrosis 12/73-PM: hepatic angiosarcoma spread to duodenum
2/74-No abnormalities	2/74-Mild elevation in LDH Liver scan: possible defect	2/74-OLB: angiosarcoma
2/74-No abnormalities	11/73-Mild elevation in TB, AP Liver scan and angiogram: 4-cm defect	2/74-OLB: angiosarcoma and extensive portal fibrosis, subcapsular fibrosis
11/68-Splenomegaly	10/68-Marked elevation in AP, BSP Mild elevation in SGOT Esophagram: varices	11/68-OLB: portal fibrosis, subcapsular fibrosis
9/71-Hepatosplenomegaly	9/71-Mild elevation in TB, SGOT 10/71-Liver scan: splenomegaly	12/71-OLB: portal fibrosis, subcapsular fibrosis
6/73-Splenomegaly	3/73-Moderate elevation in TB, AP Liver scan: splenomegaly, small liver	9/73-OLB: slight portal fibrosis
9/73-No abnormalities	9/73-Moderate elevation in SGOT Mild elevation in TB, LDH	9/73-OLB: chronic hepatitis with focal fibrosis

*TB indicates total bilirubin; SGOT, serum glutamic oxaloacetic transaminase; AP, alkaline phosphatase; LDH, lactic dehydrogenase; BSP, sulfobromophthalein.
†OLB indicates open-liver biopsy; NLB, needle liver biopsy; PM, postmortem examination.

(case 6), or angiosarcoma with extensive portal fibrosis (case 7). In cases 1 and 2, large hepatic masses were present at initial evaluation. The conditions of three patients (cases 1, 4, and 5) were not diagnosed until autopsy, despite multiple liver biopsies.

Preliminary pathologic review suggests that in all 5 patients for whom nonmalignant hepatic tissue is available (cases 2, 3, 4, 5, and 7), similar nonmalignant hepatic lesions exist, consisting of portal fibrosis, sinusoidal dilation, and atypical sinusoidal lining cells. Conceivably, such lesions may represent a precursor stage in the development of hepatic angiosarcoma.

Nonmalignant Hepatic Disease

Ages at diagnosis for these four patients (cases 8 through 11) range from 28 to 56 years (average age, 46.5). Initial clinical manifestations varied widely: one patient (case 8) had gastrointestinal bleeding; one (case 9) had chest pain and weight loss; and two patients (cases 10 and 11) had unrelated problems. On physical examination, hepatosplenomegaly was present in one patient (case 9), splenomegaly alone in two (cases 8 and 10), with normal findings in one patient (case 11). Three patients underwent splenectomy either for marked splenomegaly (case 9) or as part of splenorenal shunt procedures (cases 8 and 10). Results of liver function tests varied widely and showed no consistent patterns in relation to clinical manifestations.

All four patients were found on liver biopsy to have some degree of hepatic fibrosis. Pathologic review of specimens available from these suggests a close histologic similarity to the manifestations of portal fibrosis and sinusoidal changes described in the cases of angiosarcoma. Three patients (cases 8, 9, and 11), as well as one patient in the angiosarcoma group (case 7), were found at surgery to have a peculiar white, speckled appearance to the surface of the liver, which on pathologic section was seen to reflect diffuse subcapsular fibrosis.

EPIDEMIOLOGIC FINDINGS

The seven men with angiosarcoma had been employed at the plant for 12 to 28 years (average, 18.0), and the four with nonmalignant disease, between 5 and 29 years (average, 20.6)

Table 2.—Duration of Employment for Patients With Angiosarcoma of Liver and Nonmalignant Hepatic Disease

Case No.	Duration of Employment, yr/mo	PVC-Polymerization Buildings				Other Buildings*								Others
		A	B	C	D	E	F	G	H	I	J	K	L	
1	19/8	8/11	0/3	0	0	8/5	2/1	0	0	0	0	0	0	0
2	17/11	0/1	12/5	2/0	0	0/6	0	2/9	0/2	0	0	0	0	0
3	13/1	1/2	1/7	5/5	4/4	0	0/3	0	0	0/2	0/2	0	0	0
4	16/5	1/2	14/9	0/6	0	0	0	0	0	0	0	0	0	0
5	27/7	0/6	2/8	0	24/0	0/5	0	0	0	0	0	0	0	0
6	12/0	0	0/1	2/5	9/6	0	0	0	0	0	0	0	0	0
7	19/0	2 wk	2 wk	12/1	5/5	0	1/4	0	0	0	0/2	0	0	0
8	24/5	4/1	4/1	0	14/0	1/4	0	0	0	0	0	0/11	0	0
9	5/6	1 wk	1 wk	3/4	2/0	0	0	0	0	0/1	0	0	0	0
10	23/6	0	19/6	1/4	0	1/5	0	0	0	1/2	0	0	0/1	0
11	28/11	21/8	7/1	0/2	0	0	0	0	0	0	0	0	0	0
Total	**208/0**	**37/8**	**62/6**	**27/3**	**59/3**	**12/1**	**3/8**	**2/9**	**0/2**	**1/5**	**0/4**	**0/11**	**0/1**	**0**
No. of yr in operation	32	32	30	27	26	27	27	29	19	32	26	32	26	32†
Total No. of employees in 1973		36	36	48	40	14	1	12	0	52	72	18	8	~600

*In Building E, PVC drying and packaging are done; in F, alcohol synthesis (formerly monomer synthesis); G, PVC chlorination; H, no longer in operation (formerly monomer synthesis); I, compounding and milling; J, synthetic rubber; K, compounding (formerly warehouse and receiving); L, PVC drying.

†On the whole, other buildings were in operation as long as the plant as a whole.

Table 3.—Work Histories for Patients With Angiosarcoma of Liver and Nonmalignant Hepatic Disease

Case No.	First Liver Disease Diagnosis, Date	Total Duration of Work Before Diagnosis, yr/mo	Total Duration of Work as Chemical Helper in PVC-Polymerization Buildings, mo
1	April 1964	19/8	6
2	Aug 1967	17/11	2
3	May 1970	13/1	65
4	March 1973	16/5	20
5	Dec 1973	27/7	8
6	Feb 1974	12/0	43
7	Feb 1974	19/0	44
8	Dec 1968	24/5	47
9	Jan 1972	5/6	65
10	Sept 1973	23/6	0
11	Sept 1973	28/11	9

(Table 2). Ten of the 11 patients (cases 2 through 11) worked exclusively or predominantly in one or more of the four PVC polymerization buildings at the plant (Table 2, buildings A, B, C, and D). Patient 1 worked about half of his total employment time in a PVC polymerization building (building A) and for an almost equal time in a separate PVC drying and packaging building (building E). Three patients never worked elsewhere than in the PVC polymerization buildings (case 4, 6, and 11). As can be seen from Table 2, buildings not involved with polymerization (buildings E through L and all others) were only sparsely represented in relation to total employment. For the four polymerization buildings that in 1973 employed a total of 160 persons, 187 man-years of employment are represented among the 11 cases. For the remainder of the plant with a total employment of about 950 persons in 1973, only 21 man-years were recorded.

Buildings A and B, opened in 1942 and 1944, respectively, are the older of the four polymerization buildings; building C (1947) and building D (1948) are somewhat newer. Buildings C and D have more reactors (48 each) than either building A (35 reactors) or building B (25 reactors); the newer reactors have approximately a one-third greater capacity. Employment among all 11 patients involved all four polymerization buildings. Three patients had worked in all four buildings; five had never worked in building D, three had never worked in building A or building C, and although all 11 had worked at some time or another in building B, three had worked there less than one month. It appears unlikely that some chemical or procedure unique to any one building can be implicated as a causative factor; almost twice as many man-years of employment, however, were represented among cases for buildings B and D (121 years, 9 months) as for buildings A and C (64 years, 11 months). While this difference may or may not be meaningful, some variations do exist between the various buildings that could conceivably be important as risk factors. Buildings A and C produce homopolymer resin exclusively while various copolymers and terpolymers are produced in building B, and all PVC paste and almost all PVC latex is produced in building D.

Those workers who are probably most exposed to VCM are chemical

helpers whose principal job is to clean reactors. As can be seen in Table 3, ten of the 11 patients worked at some time as helpers. While virtually every employee at the plant has worked as a helper before being promoted to more advanced work, the average work duration (ie, time from starting work at the plant to date of diagnosis) was 23.5 years for the five patients who spent nine months or less as helpers and 15.1 years for the six patients who spent 20 months or more. This suggests indirectly a possible relationship between intensity of exposure and latent period for liver disease.

All 11 patients, or members of their immediate families, were individually interviewed regarding past hepatic disease and possible exposure to hepatotoxic agents. None of the patients had a history of hepatitis or of exposure to hepatitis, and none had taken hepatotoxic drugs. Three patients (cases 1, 7, and 9) may have had significant alcohol intake. None, except for the patient in case 7, recalled exposure to possible hepatotoxic chemicals outside the work environment, in particular to either arsenic or thorium dioxide, two chemicals previously implicated as causes of hepatic disease and hepatic angiosarcoma in humans.[4-7] Patient 7 gave a history of exposure to arsenical insecticides on the family farm between the ages of 6 and 15 years; he both mixed and sprayed the insecticides two to three times a year for about three hours on each occasion. In no case was there any history of acro-osteolysis.

COMMENT

Before the report by Creech and Johnson,[1] the only evidence that VCM might be oncogenic came from animal experiments. In 1971, Viola et al[8] published data suggesting oncogenicity of VCM when inhaled by rats at very high doses; tumors of many tissue sites, including lung, bone, and skin were recorded. Preliminary results of a more recent animal study in Italy by Maltoni et al (unpublished data) appear to indicate that angiosarcoma of liver as well as of other tissues can be induced in rats by atmospheric levels of VCM that are not uncommon in the human workplace environment. In light of these observations, it appears likely that exposure to VCM is responsible for the Louisville cases. Further support for this hypothesis is needed, of course, from additional epidemiologic data concerning workers at other PVC and VCM plants. Further toxicologic analyses are also needed to address the possibility that the active oncogenic material may be some metabolite of VCM instead of VCM itself.

Whatever the precise mechanism for oncogenicity and hepatotoxicity of VCM, the Louisville data suggest that relatively high levels of VCM exposure and relatively long intervals since first exposure (20 years or so) are involved. This does not rule out the possibility of less marked health effects at lower doses or at shorter intervals of exposure, but it does for the present focus attention on the immediate problem of assessing the health status of persons exposed in the remote past to high doses. None of the Louisville cases involved men working at the plant less than six years before diagnosis, and it can be safely assumed that levels of VCM exposure during earlier years of PVC production were considerably higher than at present because of less stringent work practice procedures and less attention to minimizing possibilities of VCM exposure in places of work.

In humans, both thorium dioxide and arsenic have previously been reported as causes both of hepatic disease and of angiosarcoma of the liver. In only one case at the Louisville plant (case 7) was there any history of exposure to either of these two materials (arsenic in insecticide spray). Likewise, there is little or no evidence among the Louisville cases that excessive alcohol intake plays any accelerating or potentially cocarcinogenic role or that any direct relationship exists between acro-osteolysis and liver disease.

Various data now suggest that VCM (or some derived metabolite) may produce in addition to angiosarcoma of the liver a nonmalignant hepatic disorder characterized by portal fibrosis and portal hypertension. This is suggested by the fact that such fibrosis was present in at least five of the Louisville tumor cases and was in addition observed in four other Louisville vinyl chloride workers without tumor. Recent observations in Germany,[9] together with earlier reports from Eastern Europe,[10] suggest that hepatic fibrosis and portal hypertension represent an occupational disease not uncommon among vinyl chloride workers. Conceivably, such fibrotic liver disease represents a premalignant state. If this proves to be so, the early detection of such liver disease may be of greater industrial and public health importance than detection of tumor itself, both because hepatic fibrosis may well emerge as a more frequent condition than tumor in vinyl chloride workers, and because it remains a possibility that very early liver abnormalities may be reversible or nonprogressive after workers have been removed from high-risk areas.

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