Original Contributions

Hepatic Disease Among Workers at a Vinyl Chloride Polymerization Plant

Henry Falk, MD; John L. Creech, Jr., MD; Clark W. Heath, Jr., MD; Maurice N. Johnson, MD; Marcus M. Key, MD

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.

(*JAMA* 230:59-63, 1974)

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support the concept that exposure to vinyl chloride monomer (VCM) may be the mechanism involved (C. Maltoni et al, unpublished data).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.

From the Cancer and Birth Defects Division, Bureau of Epidemiology, Center for Disease Control, Atlanta, Ga (Drs. Falk and Heath), the B F. Goodrich Company, Louisville, Ky (Dr. Creech) and Akron, Ohio (Dr. Johnson), and the National Institute for Occupational Safety and Health, Center for Disease Control, Rockville, Md (Dr. Key).

Reprint requests to Cancer and Birth Defects Division, Bureau of Epidemiology, Center for Disease Control, 1600 Clifton Rd, Atlanta, GA 30333 (Dr. Falk).

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-

GTR 707

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

GTR 708

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
8/[illegible]enomegaly	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.

N nmalignant 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)

GTR 709

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

GTR 710

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.

Laszlo Makk, MD, Lynn Ogden, MD, Edward Fadell, MD, Anne Richman, MD, Curtis Songster, MD, George Schrodt, MD, Edward Callahan, MD, Jerry Clanton, MD, James Kurfees, MD, Stanley Seipel, MD, and Will Ward, MD, supplied records and pathologic materials.

Louis Thomas, MD, and Hans Popper, MD, reviewed pathologic material.

References

1. Creech JL Jr, Johnson MN: Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16:150-151, 1974.

2. Wilson RH, McCormick WE, Tatum CF, et al: Occupational acro-osteolysis. *JAMA* 201:577-578, 1967.

3. Dodson VN, Dinman BD, Whitehouse WM, et al: Occupational acro-osteolysis: III. A clinical study. *Arch Environ Health* 22:83-91, 1971.

4. Da Silva Horta, Cayolla da Motta L, Abbatt JD, et al: Malignancy and other late effects following administration of Thorotrast. *Lancet* 2:201-205, 1965.

5. Da Silva Horta, Cayolla da Motta L: Followup study of thorium dioxide patients in Portugal. *Ann NY Acad Sci* 145:830-842, 1967.

6. Regelson W, Kim U, Ospina J, et al: Hemangioendothelial sarcoma of liver from chronic arsenic intoxication by Fowler's solution. *Cancer* 21:514-522, 1968.

7. Morris JS, Schmid M, Newman S, et al: Arsenic and noncirrhotic portal hypertension. *Gastroenterology* 64:86-94, 1974.

8. Viola PL, Bigotti A, Caputo A: Oncogenic response of rat skin, lungs, and bones to vinyl chloride. *Cancer Res* 31:516-522, 1971.

9. Marsteller HJ, Lelback WK, Muller R, et al: Chronisch-toxische Leberschaden bei Arbeitern in der PVC-Production. *Dtsch Med Wochenschr* 98:2311-2314, 1973.

10. Suciu F, Drejman I, Valaskai M: Etude des maladies dues au chlorure de vinyle. *Med Lav* 58:261-271, 1967.

GTR 711

Liver Damage and Angiosarcoma in Vinyl Chloride Workers

A Systematic Detection Program

Laszlo Makk, MD; John L. Creech, MD;
Joseph G. Whelan, Jr., MD; Maurice N. Johnson, MD

Recently, five cases of hepatic angiosarcoma were found in Louisville. All f the patients had worked in a plant engaged in the production of polyvinyl chl ride (PVC) from vinyl chloride. A systematic health surveillance program was instituted to detect existing liver damage or angiosarcoma and to find early signs of developing liver damage. A protocol was devised that began with on-site phlebotomies done in the plant and progressed to sophisticated h spital studies, if important abnormalities were found.

All f the 1,183 employees of the plant were tested. Two new cases of hepatic angi sarcoma and three cases of portal fibrosis were discovered by this program at the initial screening. It is hoped that continuous health monitoring will aid detection of liver abnormalities while still in a reversible or curabl state.

(*JAMA* 230:64-68, 1974)

ANGIOSARCOMA of the liver is one of the rarest human malignant neoplasms. The annual incidence in the United States is about 21 cases per year. Recently, seven cases of angiosarcoma were discovered in Louisville. These patients were scattered in various hospitals in the area and were cared for by their personal physicians. Initially, one of us noted the diagnosis of angiosarcoma of the liver on a death certificate and recalled that three years earlier he had performed a biopsy of a liver with the same diagnosis. After he found that both of these patients had worked in a plant engaged in the production of polyvinyl chloride (PVC), careful data collection was begun. Thorough search of plant and area hospital medical records resulted in the discovery of three more cases from necropsy reports recorded over a ten-year period. Two additional cases were diagnosed by biopsy in the past two months as a result of this program.

See also p 59.

Each of the patients with angiosarcoma who were under our care, and some without angiosarcoma, had fibrosis of portal areas and other pathologic changes apparent on liver biopsy specimens. None of these patients had any specific abnormal findings on physical examination or routine laboratory tests. In view of this, a systematic detection program was devised and instituted with three objectives: (1) to find any presently existing liver damage or angiosarcoma in workers exposed to vinyl chloride or its polymers, (2) to detect early liver damage, if possible while in a reversible state, with continuous health monitoring, and (3) to provide information for preventive measures.

Materials and Methods

A program was designed whereby large numbers of workers could be screened for liver disease with relative ease. The significant abnormalities were evaluated by a combined clinical, comprehensive laboratory, and roentgenographic study. The results of this evaluation served as a basis for the treatment of the patients (Fig 1). The initial laboratory procedure for detection was a 12- or 18-factor automated chemical analysis. The 12-factor analysis consisted of tests for the following: calcium, inorganic phosphorus, glucose, blood urea nitrogen (BUN), uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase (LDH), and serum glutamic oxaloacetic transaminase (SGOT). The 18-factor analysis consisted of the preceding plus creatine phosphokinase (CPK), creatinine, and serum electrolyte determinations. The blood was drawn at the plant's Medical Department; transportation, centrifugation, and test determinations were done promptly.

If the initial laboratory results were normal, the tests were repeated in three months. If abnormalities not related to the liver were found by any of the screening procedures, they were followed up according to their severity. If one liver-related abnor-

From the departments of pathology (Dr. Makk), surgery (Dr. Creech), and radiology (Dr. Whelan), St. Anthony Hospital, and the Medical Department (Drs. Creech and Johnson), B. F. Goodrich Co., Louisville.

Reprint requests to 1313 St. Anthony Place, Louisville, KY 40204 (Dr. Makk).

GTR 712

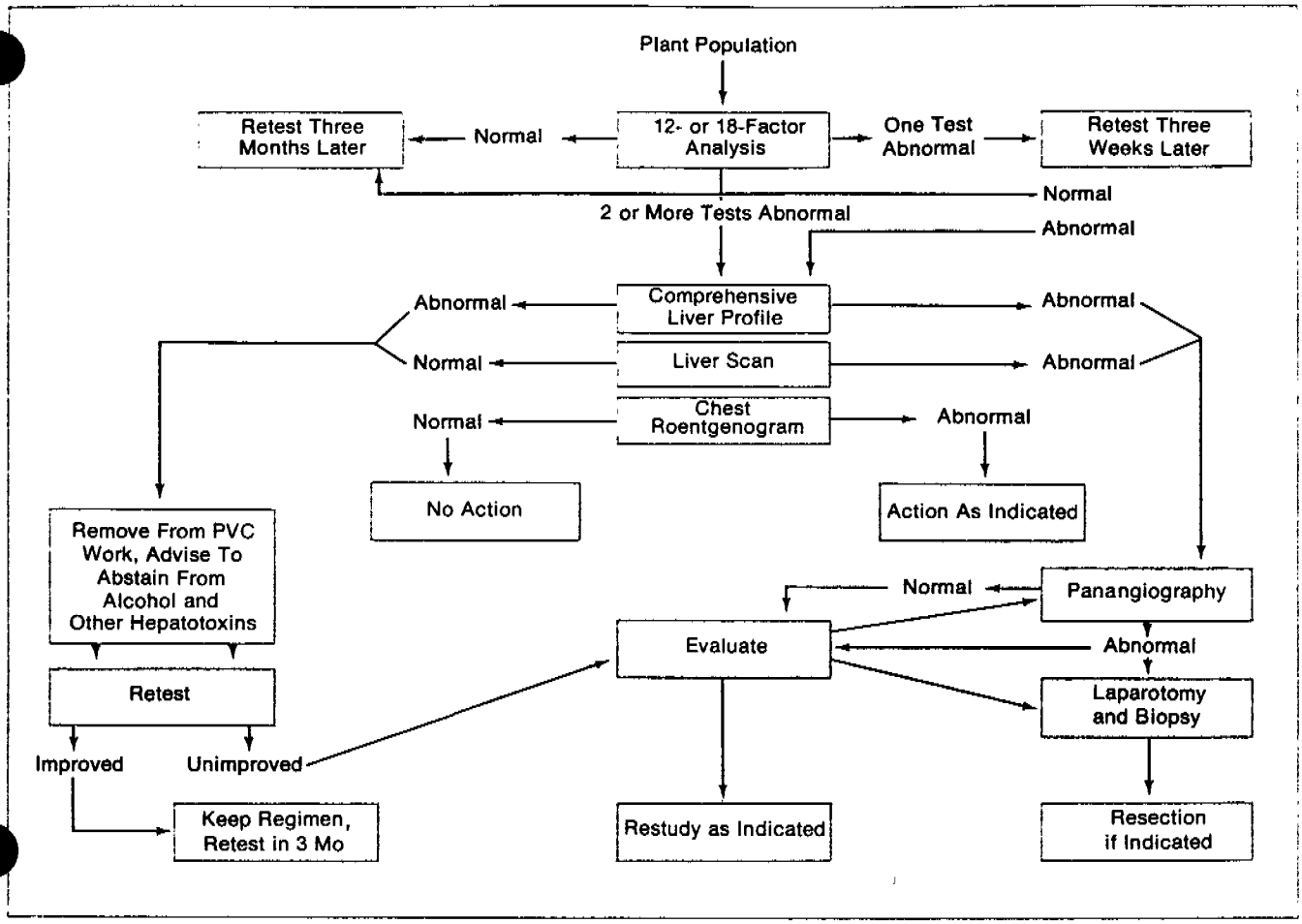


Fig 1.—Liver disease detection protocol.

mality was found, the 12-factor analysis was repeated in three weeks. If the single abnormality presisted, or if two or more liver-related abnormalities were found on the initial laboratory tests, the patient underwent a comprehensive examination consisting of tests for the following values: a 12-factor automated chemical analysis, serum electrophoresis, LDH isoenzymes, fractionated alkaline phosphatase, direct and indirect bilirubin (if total level was elevated), serum glutamic pyruvic transaminase (SGPT), γ-glutamic transpeptidase (GGTP), isocitrate dehydrogenase (ICD), α-fetoprotein (fetoglobulin), and carcinoembryonic antigen (CEA). Also, a complete blood cell count (CBC), platelet count, chest roentgenogram, and liver and spleen scan were done.

Abnormalities found in the initial 12-factor chemical analyses indicating the need for comprehensive profiles were grouped according to the following work areas: (1) PVC production, (2) synthetic rubber production, and (3) all others (including maintenance, shipping, laboratory, and other salaried employees).

Table 1.—Liver Enzyme and Bilirubin Results

Test	No. of Patients Studied	No. (%) With Abnormal Values	Normal Range	Abnormal Range
Alkaline phosphatase, mU (milliunits)/ml	72	35 (49.4)	3-85	87-135
γ-Glutamic transpeptidase, mU/ml	70	31 (44.3)	6-28	29-575
Serum glutamic oxaloacetic transaminase, mU/ml	68	19 (29.8)	4-25	27-559
Bilirubin, mg/100 ml	72	19 (26.4)	0.15-1.0	1.1-2.6
Serum glutamic oxaloacetic transaminase, mU/ml	73	13 (18.0)	12-40	48-150
Isocitrate dehydrogenase, mU/ml	59	9 (18.0)	0-7	8-88
Lactic dehydrogenase, mU/ml	72	8 (11.1)	90-225	237-475

Liver Abnormalities Dictated Hospital Studies

If abnormal scan or other findings suggested serious liver disease or the possibility of angiosarcoma, the pa-

GTR 713

Table 2.—Twelve-Factor Analysis Abnormalities and Comprehensive Screening Cases According To Work Area

Work Area	12-Factor Analysis: Total No.	12-Factor Analysis: No. (%) With Abnormality	No. (%) Comprehensive Profile Needed
Polyvinyl chloride production	274	59 (21.5)	26 (9.8)
Synthetic rubber production	203	58 (28.6)	14 (6.9)
All other	706	189 (26.7)	35 (4.9)
Total	**1,183**	**306** (26.7)	**75** (6.3)

Case No.	Diagnosis	Angiography
1	Angiosarcoma	Tumor right lobe cirrhosis
2	Angiosarcoma	Tumor, both lobes and cirrhosis
3	Portal Fibrosis, fatty change	...
4	Portal Fibrosis, moderate	Normal
5	Portal Fibrosis, slight	Normal
6	Normal	Normal
7	Normal	...

*↑ indicates elevated values; ↓, depressed values.
†N indicates normal values.

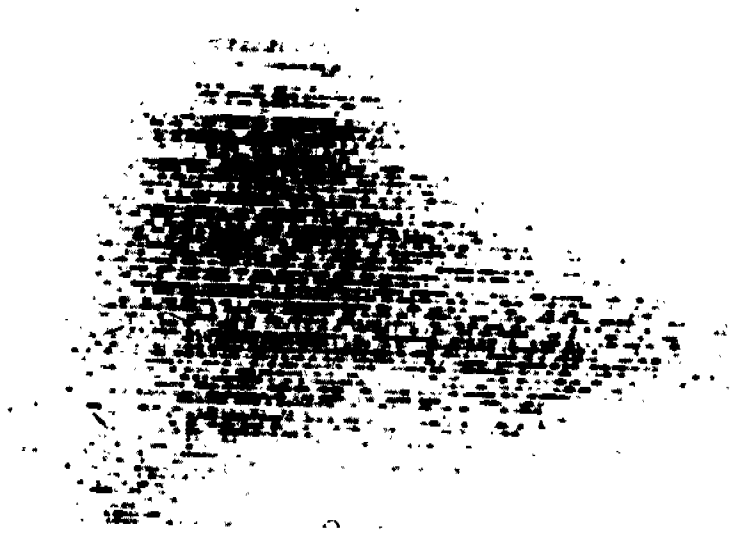


Fig 2.—Technetium 99m sulfur colloid liver scan, anterior view. Typical filling defect in right lobe of liver.

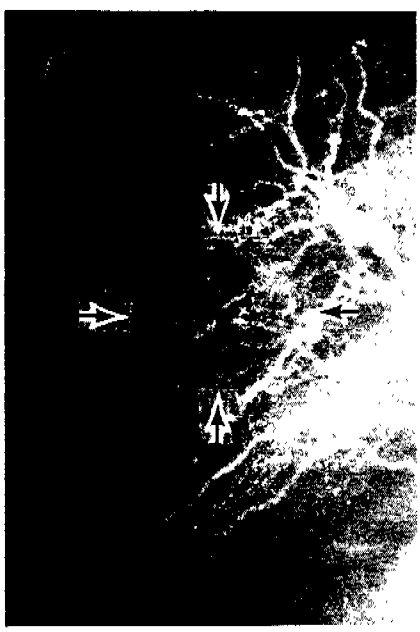


Fig 3.—Hepatic arteriogram, six seconds. Circumferential tumor vessels are present in right lobe of liver (arrows). Main hepatic artery is normal size. Intrahepatic vessels are small and tortuous suggesting cirrhosis.

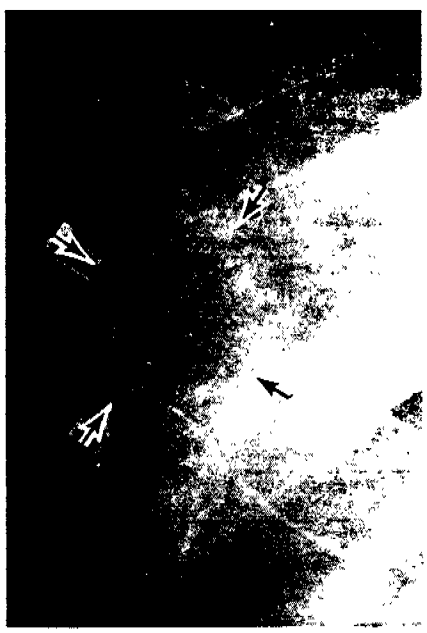


Fig 4.—Hepatic arteriogram, ten seconds, portal venous phase; Circumferential tumor stain is present with a central area of radiolucency (arrows). Stain persisted through the late portal hepatogram phase, up to 34 seconds.

tients were hospitalized and hepatic panangiography was performed, consisting of hepatosplenic arteriogram and phlebogram with free and wedged hepatic pressure measurements. The hepatic arteriogram was performed by the Seldinger technique.[1] A mixture of diatrizoate sodium and diatrizoate meglumine (Renografin-76) was used as contrast medium. If the angiograms demonstrated findings suggestive of a tumor, open-liver biopsy was advised with consideration of hepatic lobectomy, if so indicated at exploration. If angiosarcoma was limited to one lobe, a biopsy specimen of the uninvolved lobe was obtained first to evaluate the extent of fibrosis or other damage and render diagnosis by frozen section. Then, a biopsy specimen of the tumor was obtained and studied likewise.

If the uninvolved lobe had no notable disease, lobectomy of the neoplastic lobe was to be performed. If the nonneoplastic lobe was diseased (ie, showed fibrosis to a degree that lobectomy might have led to liver failure), or if the angiosarcoma involved both lobes, chemotherapy was to be considered. On biopsy, a wedge and deep Vim-Silverman needle specimen was obtained from each lobe when no gross tumor was found. In the presence of neoplasm, only wedge biopsies were taken.

Results

Screening profiles were obtained from 1,183 employees by the 12- or 18-

GTR 714

able 3.—Tissue, Roentgenologic, and Laboratory Examination Correlation

Liver Scan	Level of: Alkaline Phosphate	γ-Glutamic Transpetidase	Serum Glutamic Pyruvic Transaminase	Bilirubin	Serum Glutamic Oxaloacetic Transaminase	Lactic Dehydrogenase	Platelet Count
defect and cirrhosis	↑	↑↑	↑	↑	↑	N↑	↓
defect, both lobes	↑	↑	N	N	↑	↑	↑
tive of cirrhosis	↑	↑	↑	↑	↑	N	N
tive of cirrhosis	↑	↑	↑	N	N	N	N
tive of cirrhosis	↑	↑	N	N	N	N	N
	↑	N	N	N	N	N	N
	↑	N	N	N	N	N	N

factor chemical analysis. Of these, 75 (6.3%) had either two liver-related abnormalities on the initial screening or one such abnormality that persisted. These patients had comprehensive evaluations. One patient had initial screening in the plant, further evaluation and biopsy elsewhere, and then was transferred to our institution for further studies. Results of alkaline phosphatase, GGTP, SGPT, bilirubin, SGOT, ICD, and LDH examinations are listed in Table 1.

Significant Biochemical Findings

Other tests of the comprehensive liver profile yielded the following significant results: moderately elevated total protein values were found in three patients with a similar elevation in γ-globulin content. Serum electrophoresis showed slight to moderate increase in γ-globulin in 11 patients. The β-globulin value was slightly lowered in six patients.

In 32 patients with elevated alkaline phosphatase values, 15 had increased liver fractions. In 37 patients with normal levels of alkaline phosphatase, fractionation was also performed. Thirteen showed relative elevation of liver fractions. Eight of 72 patients (11.1%) showed elevated values for total LDH. Four of these had isoenzyme 4; two, isoenzyme 5; and one, isoenzyme 3 elevation; one had normal isoenzyme proportions.

Of 64 cases with normal LDH values, 44 showed relative elevation in level of isoenzyme 4 (68.7%); two, relative isoenzyme 5; and one, relative isoenzyme 1.

Fetoglobulin determinations gave normal results in all cases. Results of carcinoembryonic antigen radioimmunoassays were normal in all patients, with one marginal result in a patient who smoked. Complete blood cell counts disclosed normal values for hemoglobin, hematocrit, red blood cell (RBC) count, and corpuscular indexes in each patient. Four patients had slight to moderate granulocytosis. One patient showed relative lymphocytosis. Twenty-three patients showed slight, and seven moderate, monocytosis. Three patients had moderately increased eosinophil counts. One patient had thrombocytopenia with a platelet count of 98,000/cu mm, and another had thrombocytosis with a count of 750,000/cu mm (normal range, 140,000 to 440,000). The number of 12-factor abnormalities and comprehensive profiles according to work areas is listed in Table 2.

Radiological Studies

Seventy-four patients had liver scans: 11 of these scans (14.8%) were abnormal, and 2 were borderline. Six patients had filling defects (Fig 2). Three of these and another five patients had irregularities suggestive of cirrhosis. Spleen scans were performed concurrently with liver scans in 71 patients.

Three patients had had splenectomies in the past. Nine patients (12.7%) had enlargement of the spleen to 22 cm (normal spleen size is considered less than 14 cm in length[2]). Splenomegaly with abnormal liver scan was present in three patients.

Hepatic panangiography was performed in seven patients. By panangiography, two of the liver scan filling defects were found to be tumors (Fig 3 and 4). The anomalous position of the gallbladder in one case, and dilatated short gastric and collateral portal veins in another correlated with the defects on the scans. The other angiograms were normal.

Of the six splenic arteriograms, two showed splenomegaly; one of these with multiple splenic aneurysms and the other, intrasplenic arterial strictures. The other four were normal.

Surgical Findings

Exploratory laparotomy was performed in seven patients; in two, angiosarcoma was found. Resection could not be carried out in one patient because of the extent of neoplasm. In the other patient, angiosarcoma was limited to one lobe, but because of portal fibrosis in the other lobe, resection was deferred.

In three patients, varying degrees of portal fibrosis was found on laparotomy. Of the remaining two patients, one had a cholecystectomy, the other an incisional hernia repair. Liver biopsy was performed concomitantly on each. Both of these livers were essentially normal on biopsy and on laboratory testing. Correlation of biopsy, roentgenographic, and laboratory findings is given in Table 3.

GTR 715

Chest roentgenograms and laboratory examinations not related to liver function disclosed only occasional abnormalities. These were followed up appropriately. All were within the findings expected from a screening of this size male adult population. No lung tumors were found.

Comment

Nonneoplastic liver damage in polyvinyl chloride production workers has been reported.[3,4] Acro-osteolysis was also observed in such workers.[5] Viola et al[6] reported the development of skin, lung, and bone neoplasms in rats exposed to vinyl chloride. Maltoni[7] reported hepatic angiosarcomas and other neoplasms in rats exposed to high doses of vinyl chloride. To our knowledge, the Louisville cases are the first recognized human angiosarcomas of the liver associated with working in vinyl chloride monomer polymerization. Creech and Johnson[8] reported the first angiosarcoma of the liver among vinyl chloride workers. Block[9] also reported on the subject; one of our cases is included in his report. The report of Falk et al (p 59) on the epidemiology of this disease also includes two cases of angiosarcoma discovered with our program.

As the results indicate in Table 2, the percentage of abnormalities on the 12-factor examination seems higher than would be expected among a presumably healthy working population. These results also indicate that a somewhat smaller proportion of persons engaged in PVC production had abnormalities on initial 12-factor analysis than either those who worked in synthetic rubber production or all other workers in the plant. However, considerably larger numbers and percentages of the PVC workers had liver disease serious enough to warrant comprehensive profiles. All the patients who needed angiography, the two patients with angiosarcoma, and two of the three with portal fibrosis had worked in PVC production.

In our experience, the logistics of this program worked well from on-site screening to sophisticated testing. This surveillance discovered two new, otherwise unsuspected angiosarcomas of the liver and three cases of portal fibrosis. The good correlation between normal liver biopsies and essentially normal liver function tests in cases 6 and 7 was reassuring. In addition this program provided a wealth of base-line liver function test results and other health information. These data formed the basis of a continuing health monitoring program for these workers.

GGTP Reflects Extent of Damage

Of the liver function tests, the GGTP determination seemed to be most useful in detecting abnormalities and reflecting the extent of liver lesions by the degree of elevation. Alkaline phosphatase, SGPT, SGOT, LDH, and bilirubin tests were also useful. The large number of LDH^{4} isoenzyme elevations are noteworthy, but they merit further study before specific significance can be attached to them. Fetoglobulin and carcinoembryonic antigen determinations were normal. No test was specific for angiosarcoma. The liver function studies appeared to reflect quite well the extent of liver damage, except in patient 2, where this correlation was poor. He had extensive angiosarcoma and only slight elevation in LDH values on the initial screening that persisted. This prompted his astute personal physician to request more sophisticated studies and biopsy examination. It is therefore quite important than even borderline abnormalities be carefully followed up.

Scans and Angiograms

Liver scans and angiographic studies corresponded well with results of laboratory tests and biopsy examinations in the detection of cirrhosis, even in early stages. When roentgenographic studies indicated cirrhosis, the concomitant histopathologic examination disclosed a peculiar fibrosis of the portal areas instead of cirrhosis. It is our understanding that when communications refer to cirrhosis in the context of this condition, the histological findings are those of a peculiar portal fibrosis and Kupffer cell hyperplasia. Hepatic panangiography with pressure measurements as described by Viamonte et al[10] was very helpful in the differentiation of neoplastic from nonneoplastic lesions that appeared as a filling defect on scanning. It also proved helpful in the preoperative evaluation of the extent of the tumor. In addition to angiography in selected cases, we are planning liver biopsies through the right jugular vein as described by Rosch et al.[11]

The experience gained from this study enabled us to modify our method. We added GGTP and SGPT determinations to the 12-factor initial examination. Tests for fetoglobulin, ICD, and carcinoembryonic antigen as well as electrophoresis were deleted from our comprehensive profile. Until specific tests for hepatic angiosarcoma or vinyl chloride-induced liver damage are available, in our experience such a surveillance program of laboratory testing, roentgenographic examinations, and clinical evaluation will help to detect liver damage in an early, possibly reversible or curable state.

James T. Kurfees, MD, Anchorage, Ky, gave permission for inclusion of the results from one of his patients in this study.

References

1. Seldinger SI: Catheter replacement of the needle in percutaneous arteriography. *Acta Radiol* 39:368-376, 1953.

2. Siegel RM, Becker DV, Hurley JR: Evaluation of spleen-size during routine liver imaging with ^{99m}Tc and scintillation camera. *J Nucl Med* 11:689-692, 1970.

3. Marsteller HJ, et al: Chronisch-toxische-leberschaden bei arbeitern in der PVC-production *Dtsch Med Wochenschr* 98:2311-2314, 1973.

4. Suciu T, Drejam T, Valaskai M: Etude des maladies dues au chloride de vinyl. *Med Lav* 58:261-271, 1967.

5. Wilson RH, et al: Occupational acro-osteolysis: Report of 31 cases. *JAMA* 201:577, 1967.

6. Viola PL, Bigotti A, Caputo A: Oncogenic response of rat skin, lung, and bones to vinyl chloride. *Cancer Res* 31:516-522, 1971.

7. Maltoni C: Exhibit 6: Judge Myatt's hearing on oncogenic potential of vinyl chloride 43-63, 1974.

8. Creech JL, Johnson MN: Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16:150-151, 1974.

9. Block JB: Angiosarcoma of the liver following vinyl chloride exposure. *JAMA* 229:53-54, 1974.

10. Viamonte MJ, Warren WD, Foroman JJ: Liver panangiography in the assessment of portal hypertension in liver cirrhosis. *Radiol Clin North Am* 8:147-167, 1970.

11. Rosch J, et al: Transjugular approach to liver biopsy and transhepatic cholangiography. *N Engl J Med* 289:227-231, 1973.

GTR 716