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Liver Damage and Angiosarcoma in Vinyl Chloride Workers

A Systematic Detection Program

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• Recently, five cases of hepatic angiosarcoma were found in Louisville. All of the patients had worked in a plant engaged in the production of polyvinyl chloride (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 hospital studies, if important abnormalities were found.

All of the 1,183 employees of the plant were tested. Two new cases of hepatic angiosarcoma 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 curable 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-

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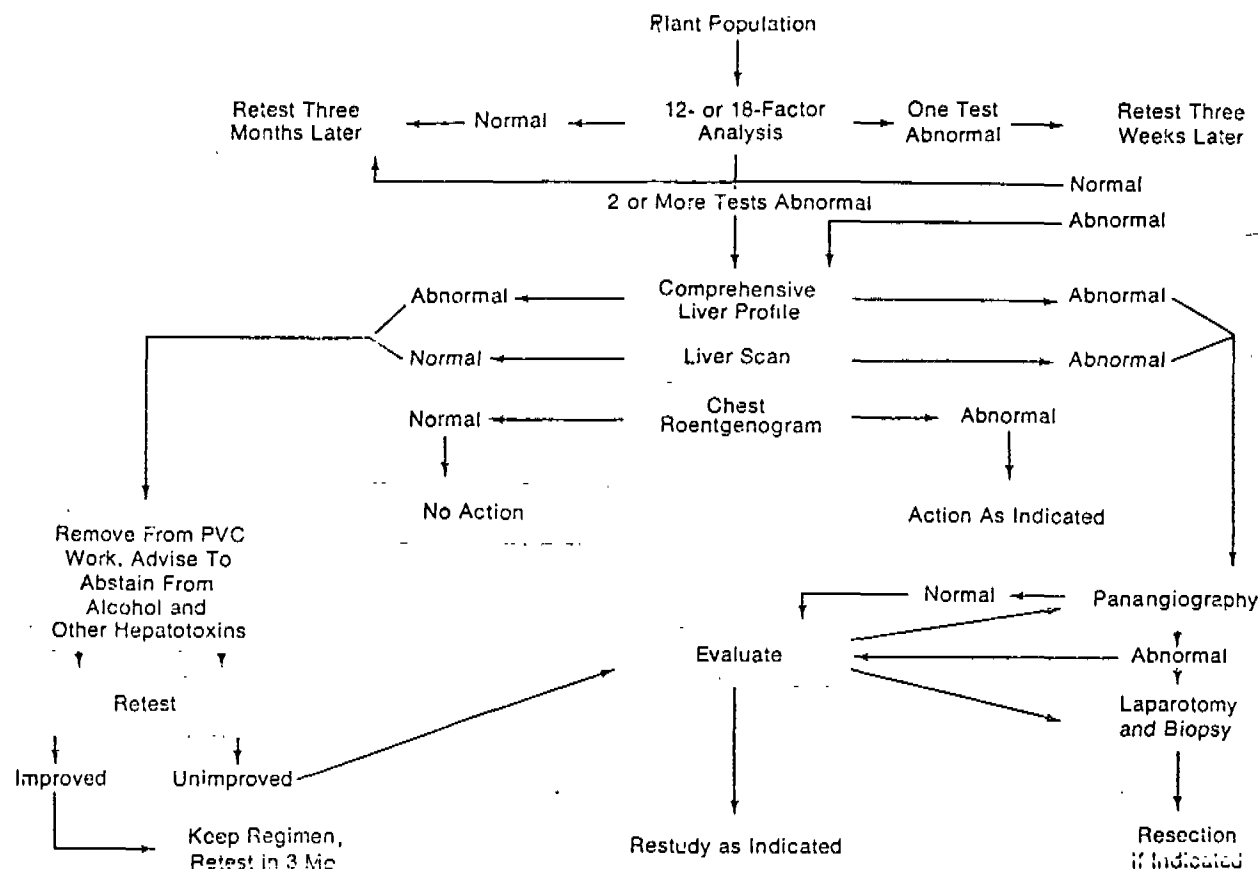


Fig 1.—Liver disease detection protocol.

mality was found, the 12-factor analysis was repeated in three weeks. If the single abnormality persisted, 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 pro-

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

files 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).

Liver Abnormalities Dictated Hospital Studies

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

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

Work Area	12-Factor Analysis		No. (%) Comprehensive Profile Needed
	Total No.	No. (%) With Abnormality	
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)

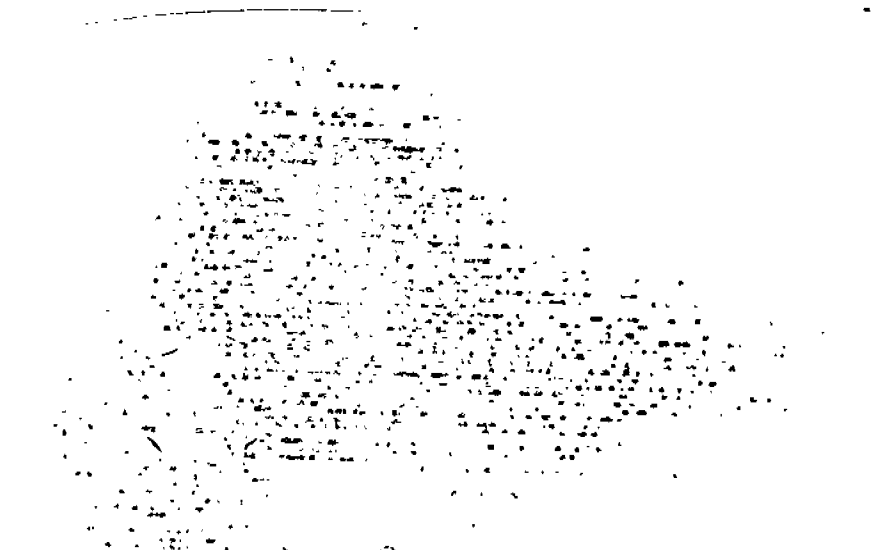


Fig 2.—Technetium 99m sulfur colloid liver scan, anterior view. Typical filling defect in right lobe of liver.

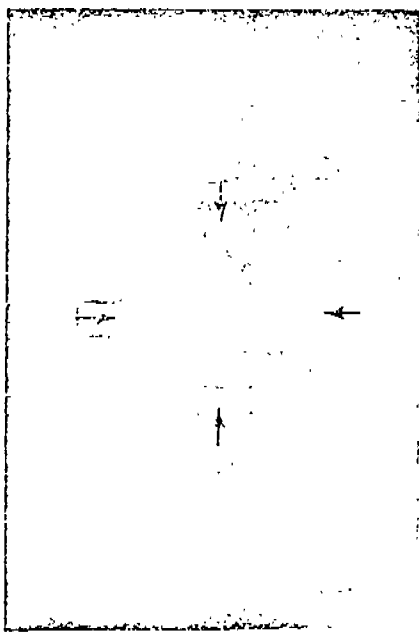


Fig 3.—Hepatic arteriogram, six seconds. Circumferential tumor vessels are present in right lobe of liver (arrows). Main hepatic artery is normal size. Intrahepatic vessels are small and tortuous suggesting cirrhosis.

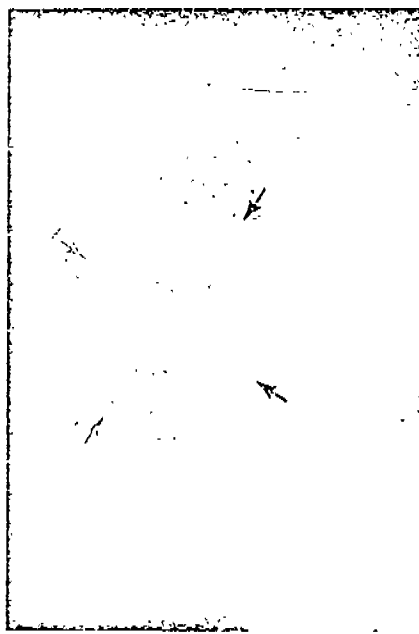


Fig 4.—Hepatic arteriogram, ten seconds, portal venous phase; Circumferential tumor stain is present with a central area of radiolucency (arrows). Stain persisted through the late portal hepatogram phase, up to 34 seconds.

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. TN Indicates normal values.

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-

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

Liver Scan	Level of						
	Alkaline Phosphate	γ -Glutamic Transpeptidase	Serum Glutamic Pyruvic Transaminase	Bilirubin	Serum Glutamic Oxaloacetic Transaminase	Lactic Dehydrogenase	Platelet Count
Filling defect and cirrhosis	↑	↑↑	↑	↑	↑	N†	↓
Filling defect, both lobes	↑	↑	N	N	↑	↑	↑
Suggestive of cirrhosis	↑	↑	↑	↑	↑	N	N
Suggestive of cirrhosis	↑	↑	↑	N	N	N	N
Suggestive of cirrhosis	↑	↑	N	N	N	N	N
Normal	↑	N	N	N	N	N	N
Normal	↑	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, CCTP, 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).

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 dilated short gastric and collateral portal veins in another correlated with the defects on the scans. 11 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.

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.^{1,4} Acro-osteolysis was also observed in such workers.³ Viola et al⁶ reported the development of skin, lung, and bone neoplasms in rats exposed to vinyl chloride. Maltoni⁷ 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 Johnson⁸ reported the first angiosarcoma of the liver among vinyl chloride workers. Block⁹ 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 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 that 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 al¹¹ 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. Kurfess, MD, Anchorage, Ky, gave permission for inclusion of the results from one of his patients in this study.

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