Occupational Carcinogenesis: The Louisville Experience with Vinyl Chloride-Associated Hepatic Angiosarcoma

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Hepatic angiosarcoma in man was first associated with exposure to vinyl chloride in Louisville, Kentucky, where it was identified in 10 persons from a single vinyl chloride polymerization plant; clinical manifestations are summarized herein. Following prolonged exposure to vinyl chloride, the onset of this disease is insidious and the clinical picture is that of nonspecific hepatic injury with mildly abnormal biochemical liver test results. Carcinoembryonic antigen and alpha fetoprotein are undetectable. Radionuclide and angiographic studies of liver show characteristic but nondiagnostic abnormalities. A definite diagnosis is usually made only by open liver biopsy. Treatment is unsatisfactory but chemotherapy seems to prolong survival. Average survival from diagnosis is about 12 months. Overt liver failure usually occurs only as a preterminal event and was the major cause of death in all of our patients. Preventive measures are now in effect in the plant. This experience illustrates the importance of the clinician in occupationally-related cancer.

Most cancers in man result from exposure to environmental factors. The occupational environment may account for as many as 10 percent of these malignancies [1]. We present the course of events and clinical findings of an industrial epidemic of hepatic angiosarcoma, a rare tumor considered to originate from the vascular lining cells of the liver [2,3]. This experience demonstrates the importance of the clinician in recognizing and controlling occupationally-induced cancer.

In 1974, several patients in Louisville, Kentucky, were found to have angiosarcoma of the liver [4]. All of these patients were men who were chemical workers at a local industrial plant that polymerizes vinyl chloride. Subsequently, additional cases in which the patients had a history of prolonged exposure to vinyl chloride were reported in Louisville [5,6] and elsewhere [7–11]. Various aspects of this malignancy including histology [11], angiographic and radionuclide characteristics [12], urine [13] and tissue [14] glycosaminoglycan patterns and epidemiologic studies [15] have been reported from Louisville. In addition, interest in this disease has propagated elsewhere, both nationally and internationally [16–18]. However, the total experience of vinyl chloride-associated angiosarcoma in the Louisville area has never been told. With a cohesive summary one begins to appreciate how the initial clinical observation of a patient with hepatic angiosarcoma led to the realization of a possible etiologic association. This, in turn, has cast a profound influence on the health of those working in a major worldwide industry involving the production of polyvinyl chloride.

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This concentration of cases of hepatic angiosarcoma gave us the opportunity to study the clinical manifestations of this unusual cancer. In view of concern regarding its increasing incidence [7,19-21], we believed a summary of this information would be valuable in detecting and managing future patients. In this paper we present the natural course, diagnosis and treatment of this disease as well as possible preventive measures that we have learned from study of the patients discovered in the Louisville area. Characteristic features of the disease, including a long period of asymptomatic laboratory abnormalities, the difficulty in diagnosis and the poor response to treatment, are demonstrated by the following illustrative case.

CASE REPORT

The patient, a 51 year old man who entered the vinyl chloride industry 28 years ago as a vat cleaner, worked in the vinyl chloride polymerization area for 18 years. During medical screening of plant employees in April 1974, he was found to have mildly abnormal serum biochemical liver test results. Liver-spleen scan disclosed no abnormalities, and he was asymptomatic.

Because of persistently abnormal biochemical liver tests, he was evaluated further in December 1974. He remained asymptomatic, and findings on physical examination were within normal limits. A hepatic angiogram showed multiple distended sinusoids throughout the liver with pooling of contrast material within these lesions. Transjugular liver biopsy specimens were histologically interpreted as showing chronic inflammatory reaction and fibrosis, attributable to the patient's previously known liver involvement with malaria. He was removed from the vinyl chloride processing area and continued active employment without symptoms.

His liver profile continued to deteriorate; by September 1975, he began to complain of tiredness and easy fatigability. The findings on physical examination remained within normal limits. Liver scan now demonstrated hepatomegaly with multiple defects throughout the liver. Biopsy specimens demonstrated sinusoidal dilatation and Kupffer cell proliferation in some of the specimens, but the diagnosis of angiosarcoma could not be made.

The patient did not return to work. His fatigue increased over the next two months and vague abdominal pain developed. In January 1976, gross hepatosplenomegaly with a bruit over the liver and signs of high output cardiac decompensation were detected. Liver-spleen scan and angiogram showed further enlargement of the previously identified lesions. An increase in arterial-venous shunting was demonstrated. At abdominal operation, direct examination revealed that the veins of the portal system were somewhat distended and that the surface of the liver was slightly nodular with some areas of bluish discoloration which were somewhat serpentine in nature. There were multiple areas on the liver in which the tissue was slightly elevated with a central depressed area of a somewhat cyanotic appearance. A strong thrill could be felt when palpating the liver. The hepatic arteries were ligated, and there was complete disappearance of the thrill.

Wedge biopsy of the liver demonstrated areas of angiosarcoma among areas of fibrosis and sinusoidal dilatation with hypertrophy and hyperplasia of sinusoidal lining cells.

Postoperatively, the cardiac decompensation was corrected and the spleen size was reduced to normal, but the liver size remained the same. Chemotherapy with doxorubicin, cyclophosphamide and methotrexate was started, and the liver was reduced to its normal size but the biochemical liver test results remained abnormal. The reduction in liver size lasted four months during which the patient was unable to carry on normal activity without fatigue. Over the next four months there was a gradual increase in the size of the liver with the development of ascites and abdominal pain with deteriorating biochemical liver test results. The patient died in December 1976 with hepatic encephalopathy and gastrointestinal bleeding. Autopsy revealed an enlarged liver with multiple small nodules of angiosarcoma throughout. The tumor was metastatic to the spleen and lungs.

BACKGROUND AND METHOD OF STUDY

Vinyl chloride is the raw material with which the common plastic polyvinyl chloride is made. Vinyl chloride monomer (CH_2CHCl) is a gas made by the reaction of ethylene and chlorine, which, when processed commercially, is polymerized in large vats under increased temperature and pressure to form a white solid. Workers are exposed to gaseous vinyl chloride by leakage from the manufacturing vats during processing, upon opening the vats after the processing is complete, or, most intensely, in the cleaning process when the worker enters the vat and chips residue off the interior wall releasing pockets of gas. Vinyl chloride was initially thought to be completely harmless, and there was no limit to the exposure workers received in the 1940s and early 1950s, however, a voluntary restriction of 50 parts per million was eventually adopted. The gas was considered to be so harmless that it was even used as a propellant in aerosol sprays [22] and a general anesthetic [23]. It gradually became apparent that prolonged exposure could induce injury in many tissues including skin, blood vessels and the reticuloendothelial system [24-26]. Evidence of liver injury was soon found [27,28], which was associated histologically with changes in the hepatocytes, fibrosis and sinusoidal dilatation [29,30]. In animal experiments, prolonged inhalation of vinyl chloride was shown to induce cancer in rats [31].

Soon thereafter an employee of the Louisville vinyl chloride polymerization plant died of hepatic angiosarcoma, but the significance of this was not appreciated until nearly two years later when a second employee also died of this rare tumor. Since these workers were cared for by different physicians at different hospitals, this might still have gone unnoticed were it not for the plant physician, whose system of requesting reports of illnesses and deaths of employees brought the diagnoses to his attention. His memory of the earlier patient with the disease led him to initiate a search for other cases among former employees and to institute a medical surveillance program of all present employees which was later supported by the National Cancer Institute and the University of Louisville. This program involved testing nearly 1,200 employees with a standard automated biochemical profile and radionuclide liver-spleen scan. Workers with persistent biochemical liver abnormalities or with abnormalities of their radionuclide scan were then examined by selective hepatic arteriography,

hepatic venography and transjugular hepatic biopsy [20,32,33].

Patients with hepatic angiosarcoma seen by the staff of the Divisions of Hematology-Oncology and Digestive Diseases and Nutrition, University of Louisville, from January 1, 1974, to January 3, 1977, include those accrued through the Vinyl Chloride Project as well as patients referred by physicians in the Louisville area and elsewhere, and a few patients found in a search of autopsy records and death certificates. A total of 11 patients have been studied, 10 of whom have had heavy industrial exposure to vinyl chloride. The other patient was a woman, referred from Florida, who had a history of prolonged use of hair spray containing vinyl chloride as a propellant. Only the 10 patients with occupational exposure to vinyl chloride are included in this report. In addition, data are derived from employee records of the Louisville vinyl chloride polymerization plant during its 35 year operation to the date of this report.

RESULTS

Epidemiology. The cohort for this analysis are the employees of the Louisville plant from its opening in 1942 to the end of 1976. The employee population has been extremely stable and during this 35 year period a total of 1,855 persons have been employed. Of these, 1,184 are current employees and 671 are past employees.

During the 35 year period, 167 members of the cohort died. Sixty-six of these died of heart disease and stroke, 39 of cancer, 19 of accidents and, nine of other disease; in 34 the cause of death could not be determined. Primary brain cancer has been related to vinyl chloride exposure [34,35], and five of the 39 deaths from cancer were from this cause. The mortality rate in our population adjusted for age is approximately twice that expected [36].

Ten cases of hepatic angiosarcoma have been identified among our 1,855 employees during the 35 year period. All of these employees worked in areas of the plant with high vinyl chloride exposure. We divided these cases into a retrospective group—cases discovered by review of hospital and pathology records, and a surveillance group—cases discovered prospectively in the surveillance program. In the retrospective group, one case each was diagnosed in 1964, 1967, 1970, 1972, 1973 and 1974. In the surveillance group, three cases were identified in 1974 and one in 1976. No other cases of angiosarcoma have been identified in the Louisville area. The incidence over the 35 year period in our cohort is 0.54 percent, equivalent to 15.4 cases per 100,000 population per year. (Predicted annual incidence in the U.S. in 0.0014 cases per 100,000 population [37].) The mean age at the time of diagnosis was 47.6 years, with a range of 36 to 58 years. All patients were white men, reflecting employment patterns at the plant. The mean duration of exposure to vinyl chloride was 17.4 years, with a range of 12 to 28 years. The mean duration from first exposure to vinyl chloride to the time of diagnosis of hepatic angiosarcoma was 19.9 years, with a range from 12 to 28 years. No differences were noted between the retrospective group and the surveillance group. Three patients had known heavy exposure to alcohol, and none of the patients had previously had viral hepatitis or exposure to any other known hepatotoxins.

TABLE I Early Clinical Features Related to Hepatic Angiosarcoma in 10 Patients

Symptoms	Patients (no.)	Signs	Patients (no.)
Pain	5	Hepatomegaly	7
Fatigue	5	Splenomegaly	5
Weakness	4	Abdominal tenderness	3
Weight Loss	3	Hepatic bruit	1
Anorexia	3		
Indigestion	1		
Abdominal fullness	1		
Melena	1		

Clinical Features. The earliest clinical features which could be related to the angiosarcoma are presented in Table I. Pain was localized in the right upper abdominal quadrant or in the lower right hemithorax. In two of the patients the pain was acute, but in the others it ranged from two to six months in duration. Fatigue and weakness had been present from one month to one year. Weight loss was significant, averaging 25 pounds over four and a half months. Hepatomegaly was the most common physical sign. The liver measured from 15 to 24 cm in total vertical span at the right mid-clavicular line by percussion. When splenomegaly was present the spleen was easily palpable 3 to 7 cm below the costal margin. Two patients, both in the surveillance group, had no physical signs, and one of these patients was asymptomatic.

Laboratory Findings. Hematologic evaluation at diagnosis showed three patients with normal complete blood counts. Mild anemia was found in five patients, but reticulocyte counts were not determined. Two of the patients had abnormal erythrocyte morphology with target cells and schistocytes. In one patient the anemia was combined with leukocytosis and in three patients with thrombocytopenia. Each patient with thrombocytopenia had splenomegaly. Two other patients had leukocytosis as their only hematologic abnormality. In two patients the bone marrow was examined: one was normal; the other demonstrated erythroid hyperplasia.

No patient was without some abnormality in at least one of the standard biochemical liver tests. Most of the values were only minimally abnormal initially. There was no consistent abnormality of any single test result or apparent pattern of groups of tests, although the alkaline phosphatase level was most frequently elevated. Hepatitis B surface antigen and alpha fetoprotein were not found in four patients who were tested, and carcinoembryonic antigen was not present in two patients.

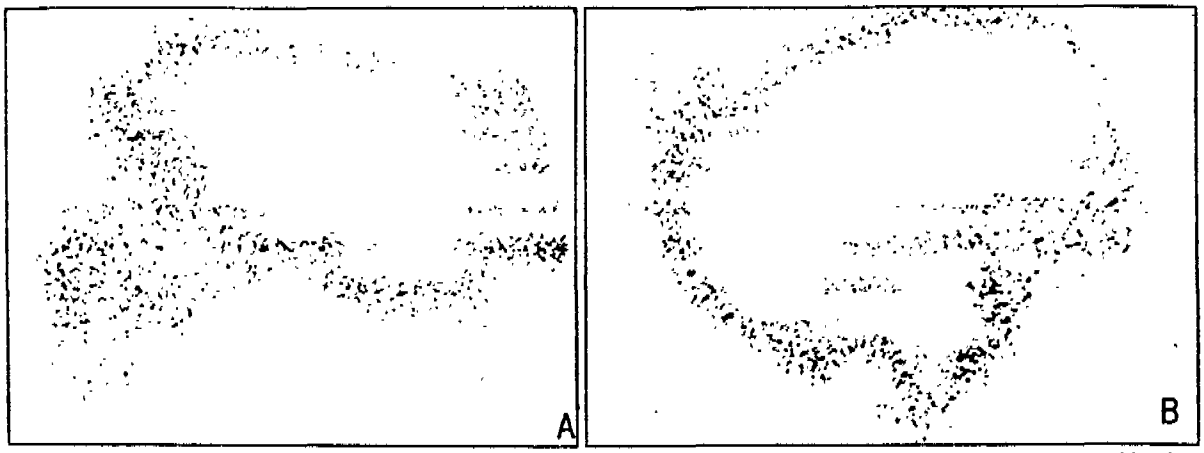

Figure 1. Liver scan in hepatic angiosarcoma. **A**, anteroposterior view. Large peripheral defect in the right lobe with other smaller defects. **B**, right lateral view.

Results of routine roentgenologic studies and gastrointestinal contrast studies were normal in most instances. However, special roentgenologic studies revealed many abnormalities. Radionuclide liver scan disclosed abnormalities in all patients; however, the abnormalities were not consistent. Six patients had hepatomegaly. In eight patients a mass was demonstrated which usally appeared as a single negative defect greater than 4 cm in diameter in the periphery of the liver. In four patients this was accompanied by one or more additional defects, and two patients had only evidence of diffuse hepatocellular disease. Typical abnormalities on liver scan are demonstrated in **Figure 1.** Splenomegaly was demonstrated in five patients by radionuclide scan. Hepatic arteriograms were obtained in six patients and demonstrated enlarged sinusoidal spaces in each of them, with a mass demonstrated in five patients. The masses were supplied by normal-sized hepatic arteries and were characterized by persistent peripheral tumor stains with some degree of central hypovascularity as shown in **Figure 2.** Hepatic ultrasound was performed in only one patient and demonstrated a solid mass.

Clinical Diagnosis. Methods: Although the signs and symptoms of our patients were fairly nonspecific, there was some finding in almost every patient that would direct one's attention to the liver in an effort to explain the clinical features. Biochemical tests of blood usually revealed nonspecific hepatic injury, but no pattern of abnormality could distinguish angiosarcoma.

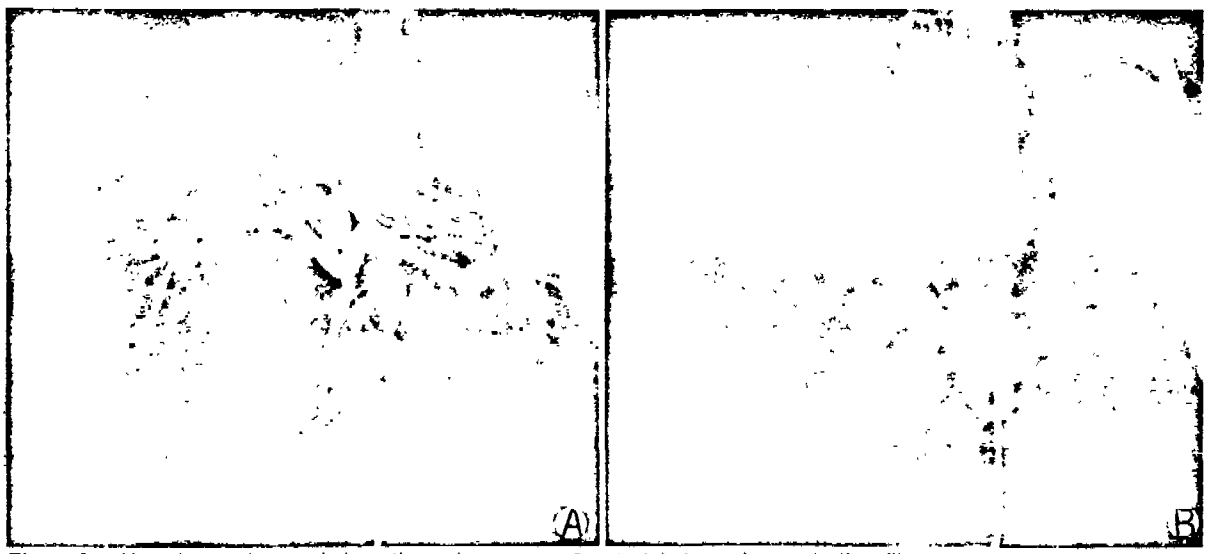

Figure 2. Hepatic arteriogram in hepatic angiosarcoma. **A**, arterial phase demonstrating dilated sinusoids in both lobes. **B**, venous phase demonstrating a large mass in the right lobe with peripheral staining and central radiolucent area.

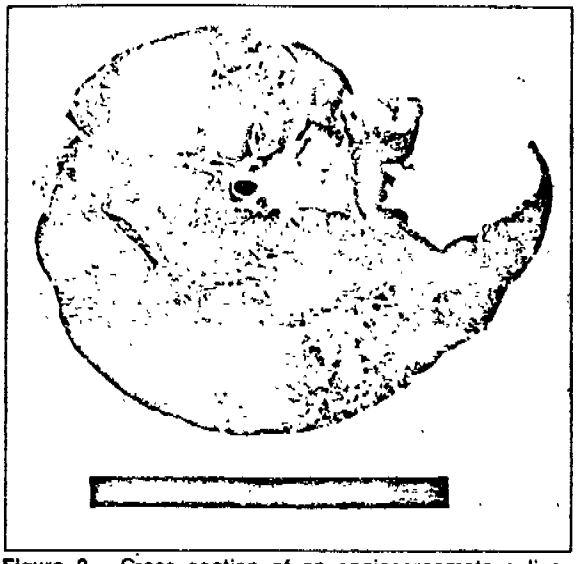

Figure 3. Gross section of an angiosarcomatous liver displaying multifocal solid and hemorrhagic cystic growth pattern with a large ruptured cyst.

The radionuclide liver scan suggested involvement of the liver by a malignant process because of the negative defect, however, the peripheral location could be mistaken for a rib impression, porta hepatis or other normal anatomic variation. The presence of multiple defects could give the impression of a malignancy metastatic to the liver. Although the liver scan frequently indicated malignancy in the liver, it was not specifically diagnostic of angiosarcoma.

The abnormal vascular pattern demonstrated by the hepatic arteriogram with the persistent peripheral tumor stain and central radiolucent area is strongly suggestive of hepatic angiosarcoma. Under unusual circumstances this appearance could mimic benign vascular lesions, liver cell adenomas or hepatic infarction. However, it is the most accurate clinical means of diagnosing hepatic angiosarcoma and should be obtained in all patients in whom the diagnosis is suspected. Further information regarding special roentgenologic studies has been detailed in the literature [12].

Extent of disease: At diagnosis the extent of disease was determined using clinical parameters and information obtained at exploratory laparotomy. In four of the patients disease was confined to one lobe of the liver and in six patients the disease involved more than one lobe of the liver. Direct extension involving the diaphragm was present in two patients and the stomach in one patient. Porta hepatis lymph nodes were involved in one patient. One patient had distant spread to the lung.

Pathology. Gross description: The liver is usually enlarged with blunt edges and a variegated brown-red-orange color. The surface may contain one or more purple-blue nodules with spongy consistency varying in size from 1 to 4 cm. In two cases these ruptured and caused hemoperitoneum. The cut surface is diffusely involved with cystic areas filled with dark blood with occasional cysts measuring up to 20 cm in diameter (**Figure 3**). In one case the tumor had a primarily solid appearance.

Definitive diagnosis: Tissue for histologic examination was obtained by percutaneous biopsy, transjugular biopsy, open liver biopsy and autopsy. Although six tissue specimens obtained by percutaneous and transjugular biopsy did identify other liver abnormalities, specimens were insufficient for accurate diagnosis of malignancy. All definitive diagnoses of angiosarcoma in this group of patients were made by tissue obtained at open liver biopsy (seven patients) and at atuopsy (three patients). In our experience, in a patient with biochemical evidence of hepatic injury with a history of prolonged exposure to vinyl chloride, open liver biopsy under direct vision is needed for diagnosis. We have no experience with laparoscopy and directed biopsy, which may be associated with less morbidity, but this approach should be tempered with caution in such a vascular tumor with major potential for hemorrhage.

Histology: All tumors were primary angiosarcoma of the liver with a wide range of patterns and differentiations seen between different tumors and within the same tumor (**Figures 4** and **5**). Areas of extensive hemorrhagic necrosis and areas of enlarged spindle-shaped endothelial cells lining irregular vascular channels appearing as a spongy network of sinusoids were present. Tumor cells occasionally projected into these channels. Large cavities lined by sarcomatous cells contained fresh or altered blood and, at times, organized clot. Three patients had histologic evidence of cirrhosis, two of whom had histories of heavy alcohol intake. One additional patient had fibrosis, and two patients had evidence of toxic hepatitis. The variable histology of angiosarcoma and the difficulties of diagnosis have been described previously [3,11,38].

Metastatic spread: Nine of the 10 patients have died, and eight of them have had postmortem examination. The single patient without a postmortem had an extensive clinical evaluation and exploratory laparotomy two weeks prior to his death. His data have been combined with the autopsy data regarding extent of disease at death. One patient with extensive hepatic fibrosis considered to be secondary to radiotherapy had microscopic angiosarcoma in the minimal remaining liver tissue with no other evidence of disease. Eight patients had extensive disease throughout the liver. Five of these eight patients had regional dissemination with involvement of diaphragm (three of five), lymph nodes (two of five), abdominal wall (two of five), gallbladder (one of five) and bowel (one of five). Four of these eight patients had distant spread with involvement of lung (four of four), bowel (two of four), adrenals (two of four), lymph nodes (one of four), brain (one of four), bone (one

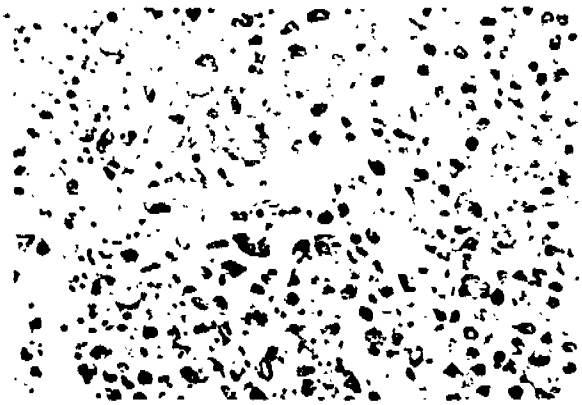

Figure 4. Undifferentiated angiosarcoma with tumor giant cells replacing the usual histologic pattern of liver tissue. Hematoxylin and eosin stain; magnification X 500, reduced 50 percent.

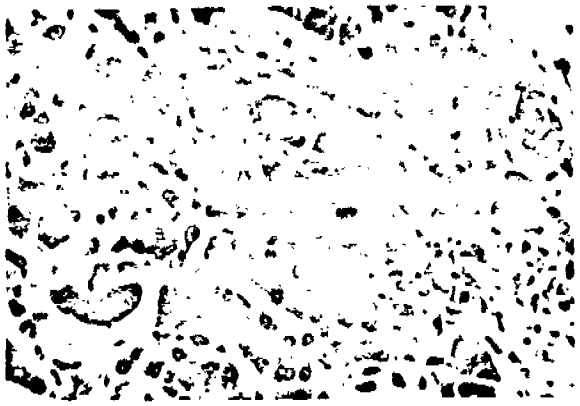

Figure 5. Multifocal minute angiosarcomatous growths are conspicuous among liver cell cords in locations distant from grossly visable tumors. Hematoxylin and eosin stain; magnification X 500, reduced 50 percent.

of four), spleen (one of four), pleura (one of four), pericardium (one of four), myocardium (one of four) and kidney (one of four). One patient had distant metastases without evidence of regional spread, and two patients had no evidence of regional or distant spread.

Therapy. In no patient was a surgical attempt at resection made. In those patients with disease confined to one lobe of the liver, fibrosis or cirrhosis in the remainder of the liver was thought to contraindicate surgery. One patient underwent hepatic artery ligation with no benefit. Radiotherapy to the liver was given to one patient early in his course with minimal tumor found at autopsy one year later, but extensive hepatic fibrosis led to his death. However, another patient, following tumor recurrence during chemotherapy, received radiotherapy seven months after diagnosis. He was found to have extensive angiosarcoma in the liver at autopsy two months later, with no apparent response to the radiotherapy. Both patients received 5,000 rads in five weeks to a major volume of the liver. Seven patients who received chemotherapy had some evidence of response by reduction in liver size or tumor size, and one patient continues to respond to chemotherapy 56 months from the time of diagnosis. Various drugs have been used individually and in combination including fluorouracil, vincristine, cyclophosphamide, doxorubicin and methotrexate.

Clinical Course. Major clinical events during the course of each patient's disease are listed in **Table II.** Congestive heart failure was preceded by a period of high output cardiac volume overload in patients with demonstrated arterial-venous shunts. Microangiopathic hemolytic anemia and platelet destruction in the peripheral blood were present without evidence of disseminated intravascular coagulopathy or sepsis, and were possibly due to cell damage in the abnormal tumor vasculature [39-42]. Symptoms of overt hepatic failure were unusual until very late in the clinical course.

The factors contributing to death in these patients are listed in **Table III.** The major cause of death was the sudden onset of irreversible rapidly progressive hepatic failure.

Survival. One patient remains alive 56 months from the time of diagnosis. Survival of the other nine patients from the time of diagnosis ranged from four months to

TABLE II **Major Clinical Events Occurring Prior to Terminal Events During the Course of Angiosarcoma Seen in 10 Patients**

Event	Patients (no.)
Pneumonia	1
Pleural effusion	1
Staphylococcal septicemia	1
Peripheral platelet destruction	2
Microangiopathic hemolytic anemia	1
Congestive heart failure	3
Renal failure	1
Hypertension	1
Gastrointestinal bleeding	1
Hepatic failure	2
Hemoperitoneum	2
Fever	1

TABLE III **Contributing Causes of Death in Nine Patients with Angiosarcoma**

Cause	Patients (no.)
Hepatic failure	9
Gastrointestinal bleeding	2
Ruptured tumor with hemoperitoneum	2
Cardiac tamponade	1
Hemothorax	1

29 months, with a mean survival of 11.7 months. When measured from the time of first symptoms, the range of survival was five months to 34 months, with a mean duration of 14.9 months. Survival from the time of diagnosis was distinctly longer in the six patients who received chemotherapy (mean 15 months) than in the three patients who did not (mean five months).

Preventive Measures. Shortly after the discovery of an epidemic of angiosarcoma in the Louisville vinyl chloride polymerization plant, new limitations of employee exposure to vinyl chloride were imposed at 1 ppm. Adherence by industry involved tighter seals on the polymerization vats and conduits which lessen leakage into the ambient atmosphere. The vat cleaning process is now performed by workers wearing protective respirators. A record keeping system has been initiated for all workers which relates length of employment and potential chemical exposure levels in each work environment to possible harm from vinyl chloride and other chemicals, so that a worker can be removed from exposure before he is likely to sustain injury. Since this process involved a change in behavior for all employees, and some jobs were more cumbersome and lengthy, an education program was designed and implemented in an effort to relieve anxiety related to work in a potentially carcinogenic environment and to promote understanding of good health maintenance. The program resulted in better cooperation with the surveillance and prevention programs. No new cases of angiosarcoma have been discovered in the Louisville plant since 1976 among 1,184 current employees and 504 past employees followed at regular intervals for four years.

COMMENTS

The Louisville hepatic angiosarcoma experience unfolds in many ways as a medical detective story. First, a fatal incident occurred. A diligent search for clues revealed vinyl chloride as a potential suspect. Further investigation and intimate cooperation among all those concerned quickly gathered sufficient evidence to incriminate vinyl chloride as the etiologic factor for hepatic angiosarcoma. The evidence included the occurrence of angiosarcoma in Louisville only in workers exposed to high concentrations of vinyl chloride over a long period of time, the discovery of similar patients in other plants producing vinyl chloride [8,9], and the production of similar hepatic lesions in experimental animals exposed to high concentrations of vinyl chloride [43,44]. The detective was an observant clinician who recognized the initial incident, realized its potential importance, instituted a systematic investigation and initiated a cancer control effort. This entire experience demonstrates the importance of the clinician in controlling occupationally-induced cancer.

The early fears of progressively increasing numbers of angiosarcoma cases related to vinyl chloride exposure [7,19–21] have not come to pass. The absence of new cases, however, should not be looked on as the end of the story. The Louisville plant is one of the oldest vinyl chloride polymerization facilities in the nation, and these workers have had the longest potential exposure to the carcinogen. In addition, because of the early lack of concern regarding exposure levels, they also have had the highest exposure. We have seen that the incubation period may range from 12 to 28 years, and it is difficult to imagine that the recently instituted preventive measures have resulted in the absence of new cases. More likely, this has resulted from the voluntary reduction in exposure levels or some other alteration in the work environment in the past. Moreover, we know that the level to which vinyl chloride exposure was voluntarily reduced is still carcinogenic [45]. We have probably seen a dose-response effect with a large number of cases occurring after exposure to a large dose. A smaller number of cases resulting from lower exposure levels will probably continue to develop in the ensuing years because of the long incubation period. This problem may become more pressing in other parts of the country in which workers in vinyl chloride polymerization plants, opened in the 1950s and early 1960s, are now nearing the mean incubation period for this disease. Mandatory restriction of atmospheric vinyl chloride levels to 1 ppm has only been in effect for five years, and it is not known whether lowering exposure levels reverses the possibility of cancer in those already exposed to higher levels. This must continue to be investigated. In the group of workers with high exposure to vinyl chloride, close surveillance should be continued indefinitely. Although the Louisville experience has revealed the close association between vinyl chloride exposure and hepatic angiosarcoma, the mechanism by which vinyl chloride triggers carcinogenesis remains to be studied through animal model experiments [46]. It is intriguing that angiosarcoma is so frequently associated with environmental factors, such as thorium dioxide [47–49], arsenic [50–52] and vinyl chloride, each of which results in stimulation of the hepatic sinusoidal lining cells [38]. Other associated factors include hemochromatosis [53–55], copper [56] and estrogens [57]. However, some cases discovered during early childhood are apparently congenital [58]. When faced with a patient with angiosarcoma without one of these recognized factors, a diligent search for other possible environmental factors should be pursued so that preventive measures can be undertaken.

Many new chemicals are introduced into our work and home environments each year. There is increasing concern that environmental factors are responsible for many cancers in man. Although sophisticated laboratory techniques and specialized knowledge are essential in cancer research, the Louisville experience in vinyl chloride-associated hepatic angiosarcoma demonstrates how a careful clinical observation followed by a well conceived clinical approach may reveal an environ-

mental etiology of neoplasia and result in profound benefit for all of us.

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