FOR ADMINISTRATIVE USE
LIMITED DISTRIBUTION
NOT FOR PUBLICATION

PUBLIC HEALTH SERVICE-CDC-Atlanta
EPI-74-63-2 May 13, 1974

TO : Director, Center for Disease Control

FROM : National Institute for Occupational Safety and Health and Cancer and Birth Defects Division, Bureau of Epidemiology

SUBJECT: Angiosarcoma of the Liver Among Vinyl Chloride Workers, Louisville, Kentucky

SUMMARY

Seven cases of angiosarcoma of the liver have been diagnosed among men employed at the B. F. Goodrich vinyl chloride polymerization plant in Louisville, Kentucky. The first case was diagnosed in April 1964. The 2 most recent cases were diagnosed in February 1974, as a result of systematic medical screening for liver abnormalities among workers at the plant. Age at diagnosis ranged from 36 to 58 (average 46.7). Duration of employment ranged from 12 to 28 years (average 17.9); all 7 men had worked in close and prolonged contact with various phases of the vinyl chloride polymerization process. Review of pathologic material from these patients suggests the presence of portal fibrosis and atypical sinusoidal cells in addition to angiosarcoma.

Four additional cases of liver disease in PVC polymerization workers at the plant (ages 28-56, work duration 6-29 years) with dates of onset ranging from 1967 to 1973 have been documented. In each case, pathologic findings of fibrosis and sinusoidal cell activity resemble those seen in the tumor cases. A direct etiologic relationship to vinyl chloride exposure is postulated for both sets of cases.

INTRODUCTION

In mid-January 1974, officials of the B. F. Goodrich Company notified the National Institute for Occupational Safety and Health (NIOSH) that 3 cases of angiosarcoma of the liver had occurred in the preceding 3 years in workers at their polyvinyl chloride (PVC) production plant in Louisville, Kentucky. A paper describing these cases has subsequently been published (1). Because of the known rarity of this tumor in the general population, and the possibility that these cases might have been occupationally induced, NIOSH decided that an immediate response was necessary and convened a preliminary investigation at the B. F. Goodrich plant in Louisville on January 24, 1974. Attending were representatives of the B. F. Goodrich Company; V. E. Rose and D. V. Lassiter of the NIOSH Office of Research and Standards Development; G. D. Nifong of the NIOSH Regional Office in Atlanta, Georgia; Ching-tsen Bien of the Occupational Safety and Health Administration (OSHA), Office of Standards, in Washington, D. C. (Department of Labor); representatives of the Kentucky Department of Labor; and Henry Falk, M.D., EIS Officer, Cancer and Birth Defects Division, located at the Texas Medical Center in Houston.

The purpose of the investigation was 2-fold: 1) for the NIOSH and OSHA representatives to conduct a preliminary walk-through of the plant to assess the PVC production process,

and to evaluate potential hazards as background for developing recommendations for interim controls, and 2) for Dr. Falk to review the medical information available on the cases of hepatic tumor.

It became apparent that a proper evaluation of the case material would also require interviews of family members and a review of medical records and pathology specimens at various hospitals. Accordingly it was agreed that Dr. Falk would undertake such detailed case reviews and that this information would be coordinated with both the NIOSH epidemiologic evaluation and with the epidemiologic evaluation which had already been started by Tabershaw, Cooper Associates, a private firm retained as occupational health consultants by the B. F. Goodrich Company.

BACKGROUND

The production of PVC from vinyl chloride monomer (VCM) began in Germany about 40 years ago, with the first United States companies (B. F. Goodrich and Union Carbide) following about 5 years later. The B. F. Goodrich Company started its first pilot unit in 1937 and opened its first full-scale plant in 1939 at Niagara Falls, New York; the Louisville plant, started in 1942, was the second full-scale Goodrich PVC plant. Rapid growth in the industry began after World War II and has continued in recent years. The average annual growth in U. S. production for the past 5 years was 14%. There are now 14 plants in the United States employing approximately 1,500 workers who produce VCM and 37 plants (owned by 23 companies) employing approximately 5,000 workers who polymerize VCM into PVC. Total U. S. production of PVC in 1972 was 4.4 billion pounds; world-wide production was over 18 billion pounds.

A rough breakdown of the varied uses of PVC is shown in Table 1:

Table 1

Estimated 1972 U. S. Market Distribution of PVC Resins

Uses of PVC	Percent
Building and construction uses of PVC (pipes, cables, exterior building products, etc.)	47.0
Home furnishings (kitchen equipment, upholstery, etc.)	14.5
Recreation (records, toys, etc.)	6.0
Transportation	6.0
Apparel	5.0
Packaging (films, bottles)	7.5
Miscellaneous	9.5
Export	3.5

There are hundreds of plants in the U. S., employing perhaps 30,000 to 50,000 workers, which utilize the PVC resins to produce this wide array of finished products.

THE LOUISVILLE PLANT

The B. F. Goodrich plant in Louisville currently has a work force of between 1,100 and 1,150 persons. Of these, 271 are considered to have potentially significant exposures to VCM. The remainder of the work force are employed in: 1) synthetic rubber production, 2) compounding and milling operations, 3) maintenance, etc., outside the PVC polymerization areas, and 4) managerial, clerical, or non-exposed salaried positions.

There are 4 separate buildings in which the PVC polymerization process is carried out; 2 were built in 1942-44 and 2 in 1947-48. Since 1942 the number of polymerization reactors and the scale of operations steadily increased until a fairly stable work

force of 250-300 PVC workers was reached in the late 1950's. This number has had only minor fluctuations since then, mostly related to market demands and production needs.

Until 1966, VCM in addition to PVC was produced at the Louisville plant. VCM was initially produced by the acetylene process (burning acetylene with hydrogen and chlorine in the presence of a mercuric chloride catalyst). This procedure was replaced in the late 1950s by a process utilizing ethylene dichloride as the starting material. No VCM has been produced at the Louisville plant since 1966.

At present, VCM is produced in a B. F. Goodrich plant in Calvert City, Kentucky, and then shipped by tank car to the Louisville plant, where it is unloaded, stored, and piped to the polymerization reactors through an essentially closed system. Each of the 4 polymerization buildings has 3 floors, and the reactors (variably called "polys," "vats," and "autoclaves") are situated on the third floor. Each reactor (ranging from 25 to 48 in each building) receives a measured amount of VCM along with the appropriate catalysts, stabilizers, emulsifiers, and additives (and other monomeric compounds if co- or terpolymers are being produced) and the reaction is carried out until the desired end-point. At the conclusion of this polymerization reaction, the suspension is dropped from the reactors to blowdown tanks on the second floor. At this point, unreacted VCM is recovered and recycled, also through an essentially closed system. The suspension then drops into blend tanks, from which it is sent to be concentrated, dried, and packaged. The end product at the Louisville plant is available in 3 basic forms: 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.

The probable point of greatest exposure to VCM for the workers occurs after the polymerization reaction when the reactors are opened and cleaned. Although the air in the reactors is replaced a number of times before opening, a short burst of VCM may be released from the reactor immediately upon opening. More importantly, some PVC remains encrusted on the walls of the reactor vessels (or on the rotors in the vessels) which, because of its porous structure, retains significant amounts of entrapped VCM. In the process of chipping and clearing this material from the reactor walls, some of the retained VCM is released. Until the late 1960s, the cleaning process was done manually by a man lowered into the reactor for that purpose; since then, high pressure water hoses have been introduced (primarily to prevent acroosteolysis, a hand disease in PVC laborers which includes Raynaud's phenomenon, scleroderma-like changes of the hands, and lytic lesions in the distal phalanges), and cleaning by hand is done less frequently.

CLINICAL HISTORIES

A thorough review of mortality data on [illegible] the Louisville plant revealed a total of 5 cases of angiosarcoma of the liver [illegible]sed in PVC workers in the 10-year period 1964-1973 (Cases 1-5, Table 2). [illegible] diagnosed prior to 1964, and no cases of angiosarcoma primary at other [illegible]ted. Two additional cases of angiosarcoma of the liver have subsequently [illegible]d among PVC workers at the plant (Cases 6 and 7) as a result of a health [illegible]rogram instituted by the B. F. Goodrich Company aimed at detecting hepatic disease, [illegible] tumors, among all current employees at the Louisville plant, whether engaged [illegible] or not. Two of the initial 5 cases (Cases 4 and 5) were first diagnosed as "[illegible] the liver" on the basis of liver biopsy specimens obtained at exploratory [illegible]. A third case (Case 3), although diagnosed as having angiosarcoma by liver [illegible]d presented with bleeding esophageal varices and a clinical diagnosis of porta[illegible]. Because of these indications of pre-existing liver disease, all workers [illegible]nt known to have had liver disease of any type diagnosed by tissue biopsy have been included in our review. Four such cases have been identified, all in PVC workers (Cases 8-11).

Table 2

Cases of Angiosarcoma of the Liver and of Non-malignant Hepatic Disease
Among Workers at the B. F. Goodrich PVC Polymerization Plant
in Louisville, Kentucky

Case Number	Age at Diagnosis, Race, Sex	Month and Year of Diagnosis	Month and Year of Death	Diagnosis
1	52 WM	Apr 1964	Apr 1964	Angiosarcoma of liver
2	43 WM	Aug 1967	Jan 1968	"
3	36 WM	May 1970	Sept 1971	"
4	49 WM	Mar 1973	Mar 1973	"
5	58 WM	Dec 1973	Dec 1973	"
6	45 WM	Feb 1974	--	"
7	43 WM	Feb 1974	--	"
8	46 WM	Dec 1968	--	Non-malignant hepatic disease
9	28 WM	Jan 1972	--	"
10	56 WM	Sept 1973	--	"
11	56 WM	Sept 1973	--	"

R S

Case #1: This 52-year-old white male was found to have angiosarcoma of the liver at the time of his death in April 1964. In August 1963, he began to note tiredness accompanied a few months later by swelling of his feet and bloating of his stomach. He was first hospitalized in January 1964 with acute onset of severe right upper quadrant pain accompanied by splinting and tenderness on physical examination. X-ray studies showed non-visualization of the gall bladder. Exploratory laparotomy and cholecystectomy were performed. At operation, free blood with clots was found upon opening the abdomen, the apparent source being a hemangioma located on the dome of the liver. The gall bladder was thickened with multiple adhesions. Histologic diagnoses indicated minimal chronic cholecystitis and focal non-specific hepatitis. Post-operative fever, icterus, and wound dehiscence required re-hospitalization, at which time liver function tests showed a total bilirubin of 4.9, direct 2.2, SGOT 115, and alkaline phosphatase normal. In February 1964, surgery was performed to drain a subphrenic hematoma and possible abscess, but the patient continued to be febrile and to bleed at the surgical site. He received 27 units of blood over a 2-month period. In March 1964, needle biopsy of the liver showed no changes in hepatic histology. X-rays and physical examinations during his course of illness showed increasing lung densities, dyspnea, and accumulating pleural fluid. The patient died on April 9, 1964. Autopsy showed massive replacement of the liver by angiosarcoma with metastasis to the epicardium, cardiac septum, lungs, pleura, serosal surfaces of small bowel and mesentery, periadrenal adipose tissue, diaphragm, and left kidney. The liver weighed 5,200 grams. The entire right lobe was replaced by tumor with many small lesions located in the left lobe, and 1,000 cc of fluid trapped above the dome of the liver. Bloody fluid was present in the pleural cavity and the pericardial sac; cardiac tamponade was the immediate cause of death.

C S

Case #2: This 43-year-old white male was found to have angiosarcoma of the liver in August 1967. During the autumn of 1966, he noted fatigue and lethargy with intermittent episodes of "pleurisy" affecting his chest and back. In July 1967, he was told by a physician that he had "anemia." In August 1967, he was hospitalized with a "knot" and severe pain in the epigastrium. Physical examination revealed a 4-finger breadth enlargement of the spleen and an epigastric mass. Laboratory studies showed hemoglobin 10, white count 7,400, and platelets 140,000. Bone marrow was normal. The patient was transferred to another hospital where laboratory studies showed platelets 33,000 and total bilirubin 1 (normal 1.0); alkaline phosphatase 31 (normal 4 to 17); SGOT 65 (normal 45); and LDH 180 (normal 120). Barium enema and lymphangiogram were within normal limits. Liver scan showed a large defect in the liver and hypersplenism was diagnosed. A

splenectomy was performed at which time a large "hemangioma or hematoma" of the liver was found and drained. Three days after operation, the patient suffered sudden abdominal blood loss which led to reoperation. Liver biopsy at that time revealed liver cancer. The patient was treated with 5-FU and cytoxan and was discharged from the hospital. The patient was readmitted in October 1967 for continued chemotherapy, but had only transient response to medication. Following a downhill course with increasing liver size, increasing ascites, and jaundice, the patient died on January 7, 1968. At autopsy, angiosarcoma of the liver was diagnosed involving both lobes with extension to the diaphragm and the anterior abdominal wall.

J.O.

Case #3: This 36-year-old white male was found to have angiosarcoma of the liver in May 1970. In January 1970 he was hospitalized because of tarry stools. Physical examination of his abdomen was negative and results of upper GI series were within normal limits. Clinical impression was bleeding duodenal ulcer, and the patient was treated with appropriate medication and diet. In May 1970, the patient was readmitted with recurrent tarry stools. Physical examination revealed hepatosplenomegaly. Laboratory studies (SMA-12) on 2 occasions showed total bilirubin 1.2 and 0.9, alkaline phosphatase 98 and 112 (normal 85), LDH 215 and 203 (normal 200), and SGOT 58 and 68 (normal 50). Upper GI series suggested a mass displacing the stomach without evidence of ulcer. An esophagogram suggested varices. Liver scan revealed a large lesion in the left lobe extending into the right lobe. A pathologic diagnosis of hepatic angiosarcoma was made on open liver biopsy. The patient was treated with 1 course of cobalt radiation in May 1970, followed by several courses of 5-FU. His clinical condition improved for approximately 1 year with weight gain, stabilizing liver function tests, and a suggestion of tumor shrinkage on repeated liver scans. In September 1971, repeat open liver biopsy showed large areas of irregular fibrosis with islands of atypical endothelial cells. The patient died on September 27, 1971, after a rapidly deteriorating course. No autopsy was performed.

E.P.

Case #4: This 41-year-old white male was first diagnosed as having liver disease ("cirrhosis") in May 1965. Angiosarcoma of the liver was diagnosed in March 1973. The patient had first been hospitalized in December 1963 because of nausea, weight loss, weakness, pallor, melena, and hematemesis. He was diagnosed as having a peptic ulcer and was treated with appropriate medication and diet. In May 1965, he was rehospitalized with repeat hemetemesis and melena. At this time, laboratory studies showed total bilirubin 0.4, alkaline phosphatase 6.7 (normal), SGOT 72, and BSP normal. Esophageal varices were visualized on esophagoscopy. Because of apparent portal hypertension with only minimal hepatic abnormalities, laparotomy was performed with a pre-operative diagnosis of possible portal vein obstruction. At operation, portal hypertension was confirmed, and a porto-caval shunt was performed. Open liver biopsy showed a low-grade process involving mild portal fibrosis, lymphocytic infiltration and scattered liver cell necrosis. Diagnosis was considered to be toxic hepatitis with possible cirrhosis secondary to work exposure to hepatotoxins. Upon return to work following discharge, the patient was transferred away from vinyl chloride work, and his liver function tests returned to normal. He was rehospitalized in November 1967 for hemorrhoidectomy and in February 1968 for repair of an inguinal hernia. In October 1970, he was hospitalized with weakness, fatigue, low-grade fever, and sweats. Physical examination showed enlargement of the liver with abnormal liver function studies. Needle biopsy of the liver revealed an aggressive form of hepatitis with progression from the previously diagnosed toxic hepatitis to cirrhosis. Later that month a cholecystectomy was performed because of gallstones. At that time open liver biopsy was interpreted as showing "very slight acute and chronic inflammation." The patient was readmitted in November and in December 1970 with increased weakness, weight loss, sweats, and fever. He was treated with steroids, but symptoms persisted. In May 1971, he was admitted to the Cleveland Clinic where an hepatic arteriogram was performed showing a "tumor blush" in the liver. At that time, the 1970 liver biopsy was re-interpreted as showing "anaplastic hepatoma and portal fibrosis." Between May 1971 and March 1973, the patient was hospitalized 6 times for chemotherapy with 5-FU and vinerlstine, as well as for symptomatic treatment of complications secondary to disease and therapy. The patient's course, however, progressed slowly downhill with incipient hepatic coma. In October 1972, the fact that liver size

had not changed for more than a year led to some doubt concerning the diagnosis of hepatoma. At that time, total bilirubin was 1.0, LDH 240, SGOT normal, and alkaline phosphatase 215, (normal values being 1.0, 85, 40, and 225, respectively). These normal values apply also to SMA-12 results cited for Cases 5-11. Liver scan showed a huge, irregular defect in the upper posterior portion of the liver. The patient expired on March 3, 1973. Autopsy showed angiosarcoma and "cirrhosis" of the liver.

E. D

Case #5: This 58-year-old white male was found to have angiosarcoma of the liver at the time of his death in December 1973. He was first admitted to the hospital in July 1973 with complaints of poor appetite, weakness, and a 25-pound weight loss over the preceding 3 months. Physical examination showed hepatosplenomegaly. Laboratory studies (SMA-12) showed total bilirubin 1.8, alkaline phosphatase 350, and SGOT 100. On repeat testing, total bilirubin was 2.4, direct 1.4. Liver scan was negative for neoplasm. Upper GI series, barium enema, and oral cholecystogram were all normal. Needle biopsy of the liver revealed "severe hepatic fibrosis with bile duct proliferation consistent with post-necrotic cirrhosis." Repeat liver scan showed hepatosplenomegaly consistent with diffuse disease. Exploratory laparotomy was then performed; no evidence of malignancy was found. At that time, multiple open liver biopsies showed periportal inflammation and fibrosis, slight bile stasis, and questionable ascending cholangitis. The patient was placed on penicillin and discharged home. He was readmitted in December 1973 with anorexia, increasing weakness, abdominal distention, and jaundice. On physical examination, he showed evidence of far advanced liver disease with marked jaundice, ascites, and spider angiomata. Laboratory studies revealed total bilirubin 35.8, direct 21.0, alkaline phosphatase greater than 350, SGOT 95 and 68 on 2 occasions, LDH 275, albumin 1.0, and prothrombin time 25.9 seconds. The patient died on December 19, 1973. Autopsy showed angiosarcoma of the liver with extension into the duodenum.

R J

Case #6: This 45-year-old white male was first found to have angiosarcoma of the liver in February 1974. Illness onset can be dated to the late summer of 1973 at which time the patient became "much more tired" than previously and also began to experience intermittent "pleurisy" under the right rib cage. In August 1973 he had a normal physical examination and normal liver function tests (SMA-12) with the exception of a slightly elevated LDH. The SMA-12 was repeated in December 1973 and February 1974 giving LDH values of 265 and 305 respectively. Because of this persistent liver function abnormality, the patient was hospitalized for extensive workup. On physical examination the liver and spleen were not enlarged. Laboratory studies showed hemoglobin 15.3, platelets normal, BSP 3%, total bilirubin 0.5, SGOT 28, alkaline phosphatase 95, LDH 311, with elevation of fraction IV isoenzymes, SGPT 19, and total protein 7.0 with increased gamma globulin and decreased albumin. Urinalysis, EKG, chest x-ray, and lung scan were all within normal limits. Liver scan showed anteriorly enlarged liver with slight diminution of uptake over the lower half of the right lobe on posterior view. Lateral views were negative. These scan results were interpreted as suspicious but not diagnostic. Laparotomy was performed. While the anterior surface of the liver appeared normal, the dome of the liver had a nodular, hard, indurated feeling, most marked posteriorly. Several open biopsies were done, and a pathologic diagnosis of angiosarcoma was made.

Case #7: This 43-year-old white male was found on SMA-12 liver function test screening in November 1973 to have mild elevations of total bilirubin (1.2) and alkaline phosphatase (133). He had no history of any symptoms except in relation to Buerger's disease affecting his lower extremities for which a lumbar sympathectomy had been performed 7 years before. There was a history of hospitalization related to increased alcohol on 2 previous occasions. Repeat screening in January 1974 showed total bilirubin normal, alkaline phosphatase 148, and SGOT 63. On hospitalization in February 1974, physical examination was normal. Hepatic scan revealed a 4 centimeter lesion in the right lobe of the liver. Hepatic angiogram showed this to be a 3x4 centimeter vascular lesion with a central radiolucent area compatible with tumor necrosis. On laparotomy, a tumor in the right lobe of the liver was identified which proved to be angiosarcoma on pathologic examination. There was evidence of extensive portal fibrosis throughout the liver.

W.M.

Case #8: This 46-year-old white male was first found to have liver disease in December 1968. In October of that year he had complained of tarry stools and weakness. Physical examination was negative except for pallor. On hospitalization hemoglobin was 5.6, and multiple transfusions were given. Liver function tests (SMA-12) revealed normal total bilirubin, LDH normal, but SGOT 75 and alkaline phosphatase 310. Upper GI series revealed x-ray evidence of duodenal ulcer. The patient refused surgery and was discharged home improved. He was readmitted in November 1968 with recurrent GI bleeding. Upper GI series suggested a lesser curvature ulcer. Vagotomy and pyloroplasty were performed. At that time the liver was described as abnormal in appearance with a whitish, splotchy capsular surface. The spleen was firm and enlarged 2 to 3 times normal size. Laboratory studies showed BSP 22%, cephalin flocculation 4+ at 24 hours, total bilirubin 1.2 direct 0.8, SGOT 114, SGPT 166, alkaline phosphatase greater than 350, and albumin normal. An esophagogram showed evidence of probable varices which were not visible on esophagoscopy. Pathologic interpretation of open biopsy material showed portal fibrosis of the liver, proliferation of bile ducts, and subcapsular fibrosis. Because of evidence of increased portal pressure, repeat laparotomy was performed, at which time a splenoportogram showed increased splanchnic pressure. Splenectomy and a splenorenal shunt were performed. The patient was readmitted in January 1969 with recurrent GI bleeding. The liver was not palpable, and liver function tests were essentially unchanged. Upper GI series in February 1969 showed varices, although somewhat less pronounced than previously. The patient was rehospitalized in May 1970 with recurrent bleeding. Liver function tests were unchanged, and BSP was 8%. He improved and was discharged home. In June 1972, he was readmitted with fever, right upper quadrant pain, and back pain. Liver function tests were normal with the exception of SGOT 220 and alkaline phosphatase 350. Liver scan was normal. A clinical diagnosis was made of pancreatic cancer; the patient, however, refused surgery. This cancer diagnosis is in doubt since the patient has remained stable clinically since that time.

J.B

Case #9: This 28-year-old white male was first found to have liver disease in January 1972. In September 1971, he was hospitalized because of chest pains and a recent 25-pound weight loss. He gave a history of some alcohol intake over the previous 6 years. Physical examination showed hepatosplenomegaly. Laboratory studies showed total bilirubin 1.9, direct 0.7, and SGOT borderline normal. ESR was 23 and 18 on 2 occasions. Monospot test was weakly positive. A diagnosis was made of possible hepatic disease secondary to alcohol intake. The patient was readmitted in October 1971, having gained 7 pounds but having developed a "butterfly rash" since his previous admission. Laboratory studies showed a negative monospot test, ESR 10, negative LE preparation, and negative anti-nuclear antibody test. Liver function tests (SMA-12) showed a slightly increased total bilirubin, normal alkaline phosphatase, and SGOT 93. Liver scan was normal except for evidence of splenic enlargement. Needle biopsy of the liver was attempted on several occasions with inadequate results. The patient was rehospitalized in December 1971 with a history of jaundice, debility, and an 8-pound weight loss. Physical examination revealed icterus, a 2-finger breadth liver and a 2-finger breadth spleen. Laboratory studies showed a normal CBC, a stool culture positive for salmonella, ESR 44, total bilirubin 5.6 and direct 4.5. SMA-12 showed bilirubin 4.3, LDH normal, SGOT 190, and alkaline phosphatase 550. Serum electrophoresis was normal. Australian antigen test was negative. An expoloratory laparotomy was performed at which time the spleen was found to be 3 times normal size, the gall bladder appeared normal, and the liver was described as having "soft dot-like disruptions of the cortex of the liver"; biopsy material showed moderate periportal fibrosis and chronic active cholangitis. The patient was readmitted in August 1973 with weight loss, melena, and hematemesis. SMA-12 was normal except for total bilirubin 1.1. Upper GI series showed a questionable peptic ulcer.

Case #10: G.A. This 56-year-old white male was found to have liver disease in September 1973. In the years prior to his diagnosis, he had had a number of liver function tests performed by the B. F. Goodrich Company during screening programs for workers exposed to vinylidine chloride. In July 1964 the patient had a negative CF test at 24 and 48 hours with total bilirubin 1.4. In March 1965, he had a 2+ CF test at 24 and 48 hours and a total

bilirubin 1.3; in April 1965, CF test was 1+ and 3+ at 24 and 48 hours with total bilirubin 0.8. In February 1973, the patient was hospitalized for bilateral hernia repair at which time he was noted to be icteric. SMA-12 at that time showed total bilirubin 3.0 and alkaline phosphatase 140, with other liver function tests normal. In March 1973, liver scan showed marked splenomegaly with a somewhat small liver suggesting cirrhosis. Cholecystogram showed a poorly functioning gall bladder. Between April and August 1973, the patient had monthly liver function tests performed which initially showed some improvement, but then worsened. In August 1973, the patient was admitted to the hospital for a work-up. SMA-12 screen was normal except for total bilirubin 2.8 and alkaline phosphatase 168. Serum electrophoresis showed gamma globulin 1.9, albumin 3.4. Liver scan showed a normal-size liver and a markedly enlarged spleen (24 centimeters). Upper GI series showed probable varices, prolonged small bowel transit time, and splenomegaly. Hepatic vein studies showed a normal venous pattern. Splenic angiogram showed marked engorgement, dilatation, and multiple aneurysms, as well as possible occlusion of the mid-portion of the splenic vein. Esophageal varices were present. Surgery was recommended but was postponed for personal reasons. The patient was readmitted in September 1973 at which time SMA-12 testing was normal except for total bilirubin 2.5 and alkaline phosphatase 133. Exploratory laparotomy was performed. The left lobe of the liver appeared normal, but an adherent veil of tortuous veins mixed with adhesions and omentum prevented both full inspection of the right lobe and palpation for possible extra hepatic portal block suggested by the operative venogram. (The multiple adhesions present in this patient were probably secondary to surgery performed in 1961 for removal of necrotic small bowel following a vascular accident.) Splenectomy and biopsy were performed. The spleen weighed 1,050 grams. A splenorenal shunt was attempted but could not be successfully completed. Pathologic examination of liver tissue showed a slight increase in portal fibrous tissue, possibly normal. In November 1973, SMA-12 liver function tests showed total bilirubin 0.7, alkaline phosphatase greater than 350, LDH 275, SGOT 43, total protein 7, and albumin 2.7.

Case #11: This 56-year-old white male was found to have liver disease in September 1973. In August 1973, he presented with a 2- to 3-week history of left lower quadrant abdominal pain. An oral cholecystogram showed gall stones. Barium enema showed diverticulosis. He was admitted to the hospital in September 1973 for cholecystectomy. Physical examination was normal. SMA-12 showed total bilirubin 1.9, SGOT 110, LDH 240, and alkaline phosphatase normal. Exploratory laparotomy was performed with cholecystectomy and liver biopsy. Operative findings included chronic cholecystitis and cholelethiasis, and a slightly enlarged liver, the surface of which was stippled with small pinhead-size "pustules" scattered throughout. No splenic enlargement was noted. There were palpable diverticuli of the colon. Pathologic examination of liver material showed subacute or chronic hepatitis with focal fibrosis and extensive regeneration. Sections of gall bladder showed chronic inflammation. Post-operatively, BSP was 12% and serum electrophoresis showed albumin 3.3. In October 1973, the patient returned to work away from vinyl chloride contact. In November 1973, the SMA-12 liver function tests were normal.

No entirely consistent pattern is apparent among the [illegible] cases with respect to presenting symptoms, physical findings, or laboratory studies, particularly with respect to liver function. Initial clinical features have varied widely, with no signs or symptoms present in Case 7. Among the persons with [illegible] patients (Cases 1, 2, 5, and 6) presented with weakness and tiredness; 2 of these also had intermittent pleuritic pain. These symptoms alone were not sufficiently severe to warrant medical evaluation until the appearance of acute abdominal pain, [illegible] weight loss, or positive findings on serologic screening. Two patients (Cases [illegible]) were entirely asymptomatic until the abrupt onset of gastrointestinal bleeding. [illegible] patients presented with clinically obvious hepatosplenomegaly (Cases [illegible]), but 4 patients (Cases 3, 4, 6, and 7) had normal physical findings. While all [illegible] patients had evidence of liver function abnormality at the time of initial workup, there was no consistent pattern, and in several instances abnormalities were only slight (Cases 2, 3, 6, and 7). In several of the tumor cases, relatively mild hepatic dysfunction coexisted with either far-advanced portal hypertension (Cases 3 and 4), unresectable angiosarcoma (Case 6) or

angiosarcoma with extensive portal fibrosis (Case 7). In Cases 1 and 2, large hepatic masses were present at initial evaluation. One patient (Case 5) had a very rapid downhill course after initial diagnosis. Three tumor patients (Cases 1, 4, and 5) were not diagnosed until autopsy despite multiple liver biopsies.

Among non-malignant cases, initial clinical presentations varied widely: 1 patient (Case 8) presented with gastrointestinal bleeding, 1 (Case 9) with chest pain and weight loss, and 2 (Cases 10 and 11) with unrelated problems. On physical examination hepatosplenomegaly was present in 1 instance (Case 9) and splenomegaly alone in 2 (Cases 8 and 10); findings were normal in Case 11. Three non-cancer 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 pattern in relation to the clinical picture. All 4 patients were found on either liver biopsy or autopsy to have some degree of hepatic fibrosis.

All of the patients or members of their immediate families were individually interviewed concerning past history of liver disease or potential exposure to hepatotoxic agents. None of the patients had a prior 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 past alcohol intake. None, except for Case 7, recalled exposure to possible hepatotoxic chemicals outside their work environment, in particular, exposure to either arsenic or thorium dioxide, 2 chemicals previously implicated as causes of hepatic disease and angiosarcoma in humans (2, 3). Patient 7 gave a history of exposure to arsenic insecticides on the family farm between the ages of 6 and 15. He both mixed and sprayed the insecticides 2-3 times during 1 month of each year for 3 hours on each occasion. He also worked for 1 year on a poultry farm with exposure to a number of fumigants and disinfectants (including formaldehyde) and in a gun powder plant (1-2 years) with close exposure to various chemicals and plasticizers.

Preliminary pathologic review of available specimens from 4 of the 7 angiosarcoma patients (Cases 2, 3, 4, and 5) suggested that all 4 had a similar appearing lesion in the non-malignant portion of their livers, consisting primarily of portal fibrosis, dilated sinusoids, and atypical sinusoidal lining cells. A similar review of specimens from all 4 non-cancer patients suggests a possibly identical picture of portal fibrosis and sinusoidal changes described in the cases of angiosarcoma. Conceivably such lesions may represent an intermediate state in the development of hepatic angiosarcoma. Four patients (Cases 7, 8, 9, and 11) were found at surgery to have a peculiar white, speckling on the surface of the liver, which on pathologic section was seen to reflect diffuse subcapsular fibrosis. This is an unusual lesion and may perhaps represent a pathognomonic feature in the pathologic picture.

WORK HISTORIES

Ten of the 11 patients (Cases 2-11) worked exclusively or predominantly in 1 or more of the 4 PVC polymerization buildings at the plant (Table 3, Buildings A, B, C, and D). Patient 1 worked for about the first 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 PVC polymerization buildings (Cases 4, 6, and 11). As shown in Table 3, non-polymerization buildings (Buildings E-L and all others) were only sparsely represented in relation to total employment. For the 4 polymerization buildings which in 1973 employed a total of 160 persons, 184 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.

Table 3

Duration of Employment for Patients With Angiosarcoma of the Liver and Non-malignant Hepatic Disease Among Workers at the B. F. Goodrich PVC-polymerization Plant in Louisville, Kentucky, by Building of Employment

Case Number	Total Duration of Employment	PVC polymerization Buildings				Other Buildings*								
		A	B	C	D	E	F	G	H	I	J	K	L	Others
1	19 yr/8 mo	8/11	0/3	0	0	8/5	2/1	0	0	0	0	0	0	0
2	17 yr/11 mo	0/1	12/5	2/0	0	0/6	0	2/9	0/2	0	0	0	0	0
3	13 yr/1 mo	1/2	1/7	5/5	4/4	0	0/3	0	0	0/2	0/2	0	0	0
4	16 yr/5 mo	1/2	14/9	0/6	0	0	0	0	0	0	0	0	0	0
5	27 yr/7 mo	0/6	2/8	0	24/0	0/5	0	0	0	0	0	0	0	0
6	12 yr/0 mo	0	0/1	2/5	9/6	0	0	0	0	0	0	0	0	0
7	19 yr/0 mo	2 wk	2 wk	12/1	5/5	0	1/4	0	0	0	0/2	0	0	0
8	24 yr/5 mo	4/1	4/1	0	14/0	1/4	0	0	0	0	0	0/11	0	0
9	5 yr/6 mo	1 wk	1 wk	3/4	2/0	0	0	0	0	0/1	0	0	0	0
10	23 yr/8 mo	0	19/6	1/4	0	1/5	0	0	0	1/2	0	0	0/1	0
11	28 yr/11 mo	21/8	7/1	0/2	0	0	0	0	0	0	0	0	0	0
Total	208 yr/0 mo	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. yrs 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	about 600

*E - PVC drying and packaging
F - formerly monomer synthesis - now alcohol synthesis
G - PVC chlorination
H - formerly monomer synthesis - no longer in operation
I - compounding and milling
J - synthetic rubber
K - formerly warehouse and receiving - now compounding
L - PVC drying

Buildings A and B are the older of the 4 buildings (opened in 1942 and 1944, respectively); Building C (1947) and Building D (1948) are somewhat newer. Buildings C and D have more reactors (48 each) than Buildings A (35) and B (25); in addition, the newer reactors have an approximately one-third greater capacity. Employment among the 11 patients involved 4 polymerization buildings: 3 patients had worked in all 4 buildings, 5 had never worked in Building D, 3 had never worked in Building A or Building C, and although all had worked in Building B at one time or another, 3 had worked there less than 1 month. It appears unlikely, therefore, that some chemical or procedure unique to any 1 building can be implicated as a causative factor. More than twice as many man-years of employment, however, were represented among cases for Buildings B and D (121 years, 3 months) than for Buildings A and C (63 years, 3 months). While this difference may or may not be meaningful, some variations do exist between the various buildings which could conceivably be important as risk factors. Buildings A and C produce homopolymer resin exclusively while various co- and ter-polymers are produced in Building B, and PVC paste and almost all PVC latex is produced in Building D. In addition to differences both in the amount of VCM that may physically be retained by these various products, and in terms of additional chemicals used in producing co-polymers, there may be significant differences in work practices related to the various products--e.g., a latex reactor may be more difficult to clean and may take longer than a resin reactor, while a glass-lined reactor may take a different length of time to clean than a stainless steel-lined reactor. All such factors deserve further consideration as additional data are developed concerning disease occurrence in the Louisville plant and elsewhere.

The workers who are probably most exposed to VCM are the "chemical helpers" whose job it is to clean the reactors. As shown in Table 4, all 11 patients worked for some time as helpers; indeed, virtually every employee at the plant had worked initially as a helper for some time before being promoted to more advanced work (trainee or chemical operator). The average work duration (i.e. time from starting work at the plant to date of diagnosis) was 23.2 years for the 5 patients who spent 14 months or less as helpers, and 15.0 years for the 6 patients who spent 20 months or more.

Table 4

Work Histories for Patients with Angiosarcoma of the Liver and Non-malignant Hepatic Disease Among Workers at the B. F. Goodrich PVC-polymerization Plant in Louisville, Kentucky

Case Number	Date of Diagnosis	Total Duration of Work Prior to Diagnosis (Years/Months)	Total Duration of Work as Chemical Helper in PVC-polymerization Buildings (Months)
1	Apr 1964	19/8	6
2	Aug 1967	17/11	2
3	May 1970	13/1	51
4	Mar 1973	16/5	20
5	Dec 1973	28/0	8
6	Feb 1974	11/10	43
7	Feb 1974	18/0	32
8	Dec 1968	24/5	47
9	Jan 1972	5/6	58
10	Sept 1973	23/8	14
11	Sept 1973	28/11	9

DISCUSSION

Preliminary results of animal experiments currently being conducted by Professor Cesare Maltoni, Director, Institute of Oncology, in Bologna, Italy (4), strongly implicate VCM at concentrations which are not uncommon in the workplace as a cause of angiosarcoma in rats, both in liver and at other sites. It seems likely, therefore, that VCM is the causative agent in the Louisville cases, although this remains to be supported by epidemiologic data from other PVC plants.

In humans, both thorium dioxide and arsenic have previously been implicated as causes both of angiosarcoma and of non-malignant hepatic disease (2-3). Since all of the cases at the Louisville plant, malignant and non-malignant diseases alike, were similar in terms both of clinical symptoms and of fibrotic and cytologic changes in liver, it seems likely that a single disease process is involved which presents primarily with portal fibrosis and sinusoidal changes, and which, in a certain percentage of cases, progresses to angiosarcoma. At what point and under what conditions malignancy develops and the disease process becomes irreversible is not yet clear. Removal from occupational VCM exposure in the early stages may possibly arrest or conceivably even reverse the disease progression.

The silent, asymptomatic course which the disease appears to follow, and the fact that abnormalities of liver function testing appear to be a relatively late manifestation pose a major problem for the development of effective medical screening of workers exposed to VCM. For screening to be truly effective, it may be necessary for new screening procedures to be designed which can detect the disease process in its early stages, i.e., early evidence of portal hypertension, portal fibrosis, and/or hepatic sinusoidal cell changes.

Plans for future study of this disease problem by NIOSH and the Bureau of Epidemiology, CDC, include the following areas with respect specifically to the Louisville plant. This work is being pursued in collaboration with the B. F. Goodrich Company, Tabershaw, Cooper Associates, Inc., the University of Louisville, and the National Institutes of Health within the context of a larger NIOSH/CDC study which involves the investigation of several other PVC polymerization plants located elsewhere in the United States:

1) A continuing review of clinical and pathologic material derived from all cases of hepatobiliary disease as they are discovered at the Louisville plant.

2) A review of all deaths among workers at the Louisville plant, aimed at defining the full spectrum of VCM/PVC-related disease.

3) A review of all available autopsy and biopsy material from past workers at the Louisville plant to define the prevalence of hepatic abnormalities both in PVC polymerization workers and in other chemical workers.

4) An evaluation of medical screening data with the goal of developing the most appropriate screening procedures possible.

REFERENCES

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

2. da Silva Horta J, Abbatt JD, Cayolla da Motta L, Roriz ML: Malignancy and other late effects following administration of Thorotrast. Lancet 2:201-205, 1965

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

4. Maltoni C: unpublished observations

Henry Falk

Henry Falk, M.D.
EIS Officer
Cancer & Birth Defects Division
Bureau of Epidemiology

Clark W. Heath

Clark W. Heath, Jr., M.D., Director
Cancer & Birth Defects Division
Bureau of Epidemiology

Marcus M. Key

Marcus M. Key, M.D., Director
National Institute for Occupational
Safety and Health

DISTRIBUTION
Mailing keys 53-1, 2, 3
Maurice N. Johnson, M.D., Director, Environmental Health, B. F. Goodrich Company, 500 South Main Street, Akron, Ohio 44311
John L. Creech, Jr., M.D., Plant Physician, B. F. Goodrich Company, Post Office Box 954, Louisville, Kentucky 40401
Hans Popper, M.D., Fogarty International Center, National Institutes of Health, Bethesda, Maryland 20014
Louis B. Thomas, M.D., Chief, Laboratory of Pathology, National Cancer Institute-NIH, Building 10, Room 2A29, Bethesda, Maryland 20014
Dr. Bradford Block, State Department of Labor, Frankfort, Kentucky 40601
Calixto Hernandez, M.D., State Epidemiologist, State Department of Health, Frankfort, Kentucky 40601
Dr. Joseph K. Wagoner, Director, Division of Field Studies and Clinical Investigations, NIOSH, 1014 Broadway, Cincinnati, Ohio 45202
Dr. J. William Lloyd, Acting Assistant Director for Health Surveillance and Biometrics, NIOSH, Room 10A-30, Parklawn Building, Rockville, Maryland 20852