Virchows Arch. A Path. Anat. and Histol. 372, 195–203 (1976)

Virchows Archiv A

Hemangiosarcoma and Hepatocellular Carcinoma of the Liver Following Vinyl Chloride Exposure

A Report of Two Cases

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Summary. A report is given of the clinical and autopsy findings of two men who died from malignant liver neoplasm following occupational exposure to vinyl chloride. The first patient was a 44-year-old man with an hemangiosarcoma of the liver, the second patient a 67-year-old man with an hepatocellular carcinoma. So far an hepatocellular carcinoma due to vinyl chloride has not yet been observed in man. Its occurrence, however, has been suggested from the results of animal experiments. The connection of hepatocellular carcinoma with exposure to vinyl chloride is discussed.

Key words: Vinyl chloride – Occupational exposure – Hemangiosarcoma and hepatocellular carcinoma of the liver.

Zusammenfassung. Es wird über zwei bösartige Lebererkrankungen nach beruflicher Exposition von Vinylchlorid berichtet. Dabei handelt es sich um ein typisches Haemangiosarkom bei einem 44 Jahre und ein hepatocelluläres Carcinom bei einem 67 Jahre alt gewordenen Chemiearbeiter. Bis jetzt ist ein hepatocelluläres Carcinom nach gesicherter Vinylchloridexposition beim Menschen nicht beobachtet worden. Hepatocelluläre Carcinome nach Vinylchloridexposition waren jedoch aus tierexperimentellen Untersuchungen bekannt und ihr Vorkommen auch beim Menschen vermutet worden.

Introduction

Vinyl chloride (VC), a colorless, flammable and explosive gas, has been used as a monomer for the polymerization process of polyvinyl chloride (PVC) for more than 30 years. PVC nowadays is the plastic industrial material most used in the world. It is also used as a copolymer in other plastics, as a chemical intermediate, as a solvent, and as a propellant. VC has been thought to be biologically inert. However, observations of skin, bone, spleen, and liver changes in workers who were exposed to VC for various periods, report by Suciu et al. (1963, 1967), Cordier et al. (1966), Harris and Adams (1967), Wilson

et al. (1967), Marsteller et al. (1973), Lange et al. (1974), Falk et al. (1974) and Thomas et al. (1975), have demonstrated that VC is not altogether harmless. In 1974 Creech and Johnson published the first report indicating that hemangiosarcoma of the liver may have a causal relation to employment in the manufacture of polyvinyl chloride resins.

We present a case of a fatal hemangiosarcoma of the liver due to occupational VC exposure. We also describe the history, clinical, and autopsy findings of a man who was exposed to VC and who died from hepatocellular carcinoma.

Report of Cases

Case 1

The patient, a 44-year-old man, was employed in the manufacture of polyvinyl chloride from 1957 until 1974. During this period he worked at several places in the polymerization process and was exposed to VC at 200–500 ppm. For approximately 1 year (1958) his job involved cleaning the reactors in which VC was polymerized. During the cleaning process he was exposed to high concentrations of VC. He had no history of hepatitis, exposure to hepatitis or significant alcohol intake. He had never taken hepatotoxic drugs.

In September 1968 he developed mild jaundice which responded well to conservative medical treatment. In February 1971 he was treated in a clinic for mild hypertension, overweight and low back pain. On clinical examination the liver and spleen were firm and slightly enlarged. Laboratory investigation showed mild hepatic dysfunction with a slight elevation of urobilinogen and bilirubin. Prothrombin activity was 75%. The total and differential blood count was normal except for a diminished platelet count of 72,000/ccm. A laparoscopy was performed, which revealed a slightly enlarged, firm liver with a peculiar, white speckled and finely granular surface. The gastric veins were tortuous and dilated, indicating portal hypertension. No free fluid was found in the peritoneal cavity. A liver biopsy was taken, which showed portal and septal fibrosis of the parenchyma. The hepatocytes varied slightly in size and shape and the Kupffer cells appeared activated. They showed focal proliferation, forming small cell clusters. A diagnosis of liver cirrhosis was made.

In the autumn of 1974 the patient complained of increasing pain in his left shoulder girdle, for which he was readmitted to hospital in November 1974. On clinical examination slight atrophy of the left trapezius muscle was found and a loss of sensitivity over the outer part of the left forearm was noted. He showed marked tenderness on pressure over the lower cervical and the upper thoracic vertebrae. Liver function tests showed a slightly raised total bilirubin and marked elevation of lactic dehydrogenase and serum oxalacetic transaminase. The sulfobromphthalein excretion was reduced. Prothrombin activity was 50% and the platelet count was 65,000/ccm. On the 20th day after admission he suddenly complained of severe pain in the right upper abdomen and developed signs of clinical shock, which was rapidly progressive. Proposed laparotomy for the clinical diagnosis of intraabdominal hemorrhage could not be performed because of the intractable severe shock. The patient failed to respond to treatment and died.

Autopsy. At autopsy massive hemorrhage into the peritoneal cavity (3500 ml) was found. The liver was enlarged (weight 2650 g) and showed extensive rupture of the right lobe. The liver surface showed reddish-brown bulging masses, which, on section, were found to almost entirely replace the liver tissue and consist of large, blood-filled nodules, which coalesced and measured up to 10 cm in diameter. Microscopic examination of the tumor tissue showed blood-filled cavernous spaces and sinusoidal channels with areas of necrosis and hemorrhage. The vascular spaces were lined by spheroidal and spindle-shaped cells with

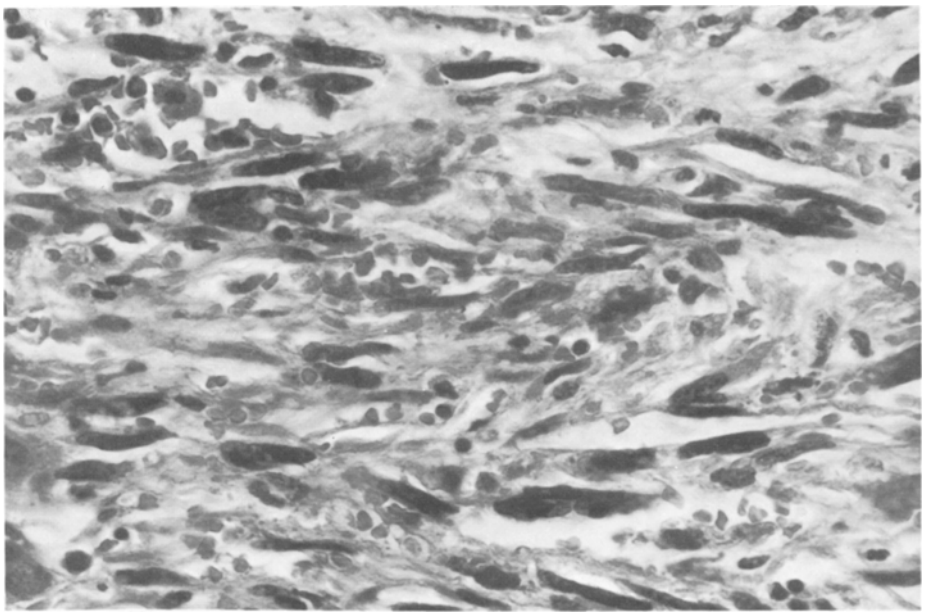

Fig. 1. Histologic section of hemangiosarcoma of liver with malignant pleomorphic endothelial cells forming irregular vascular spaces. H&E, ×210

multiple, bizzare nuclei (Fig. 1). Mitoses were frequent. In the channels few foci of hematopoiesis were noted. The margins between the liver and the neoplastic tissue were irregular and indistinct, with invasion of the liver along preexisting sinusoids (Fig. 2). In addition to the cavernous and sinusoidal growth pattern, nodules of anaplastic sarcoma cells were found. In some areas the liver tissue was compressed by these tumor nodules to form a pseudocapsule. The diagnosis of multicentric hemangiosarcoma of the liver was made. The remainder of the liver showed irregular areas of fibrosis involving the hepatic capsule and the portal tracts. The first thoracic vertebra was partially destroyed by metastatic hemangiosarcoma, which compressed the nerves in the left intervertebral foramen and infiltrated the paravertebral muscles. The spleen was markedly enlarged (weight 830 g) and showed capsular fibrosis. On microscopic examination subcapsular areas of fibrosis and reticuloendothelial proliferation of the type seen in portal hypertension were obvious. Atypical cells were not found. There was dilatation of the submucosal veins in the esophagus and cardia.

Case 2

The patient, a 67-year-old man, was employed in a PVC polymerization plant from 1949 until he retired in 1972. For 14 years he was employed in the production of polyvinylacetate. According to the information obtained from the factory management he should not have been exposed to VC in this particular production area but data of VC concentration in the working environment are lacking. His previous health had been good until 1965, when he was hospitalized for about

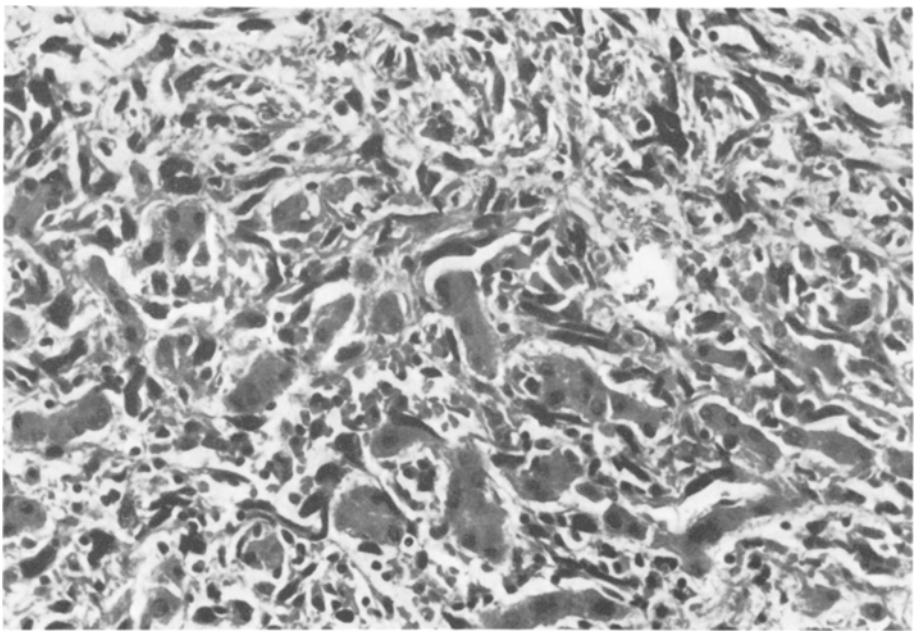

Fig. 2. Hemangiosarcoma of liver infiltrating liver tissue along preexisting sinusoids. H&E, ×330

6 months with tuberculosis of the apical lobe of the right lung. He was treated with streptomycin, isoniazide and aminosalicylic acid. After 1 year of convalescence he returned to the plant and was employed as a carrier in the PVC polymerization area until 1968. During this period he was occasionally exposed to VC of unknown concentration and duration. He was then transferred to the laboratory of physical examination, where he worked until his retirement in April 1972. During this work he was exposed to VC at 200 ppm maximum. He was admitted to hospital in January 1973 for cavernous tuberculosis of his right lung and was given a course of treatment of rifampin, isoniazide and ethambutol. Laboratory investigation in July 1973 showed a mild liver dysfunction which was thought to be due to liver cirrhosis. Information solicited from relatives, physicians and fellow workers gave no history of hepatitis or significant alcohol consumption.

The patient was hospitalized in July 1975 with cachexia and rapidly progressing ascites. Laboratory investigations revealed a hypochromic, normocytic anemia and a normal platelet count. The prothrombin activity was 70%. Serum glutamic oxalacetic transaminase and gamma glutamic transpeptidase were slightly elevated. Sulfobromphthalein excretion was markedly reduced. He did not respond to diuretics and the hemoglobin concentration gradually fell. Hemorrhagic fluid was obtained by diagnostic paracentesis. In view of his poor general condition laparotomy or further treatment was not feasible and he died 6 days after admission.

Autopsy. On opening the abdomen, rupture of the left liver lobe was found with 2000 ml bloody fluid in the abdominal cavity. The liver was markedly enlarged and weighed 2900 g. The surface was bosselated, and cut sections showed the entire liver tissue nearly completely replaced by yellow-brown nodules measuring from 5 to 20 mm in diameter (Fig. 3). Many nodules appeared encapsulated and displayed hemorrhage and necrosis. Microscopic examination revealed a multicentric hepatocellular carcinoma. Under low magnification most areas of the tumor tissue showed a trabecular growth pattern with a small capillary stroma (Fig. 4). In other areas nodules of closely packed pleomorphic

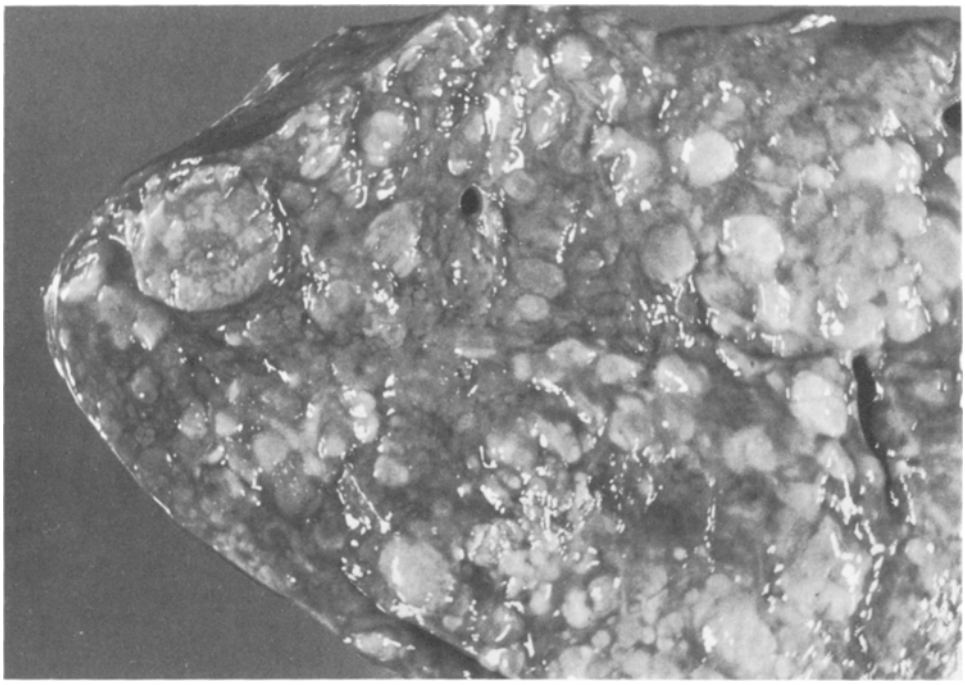

Fig. 3. Cut section of liver showing multiple tumor nodules of an hepatocellular carcinoma nearly completely replacing liver tissue

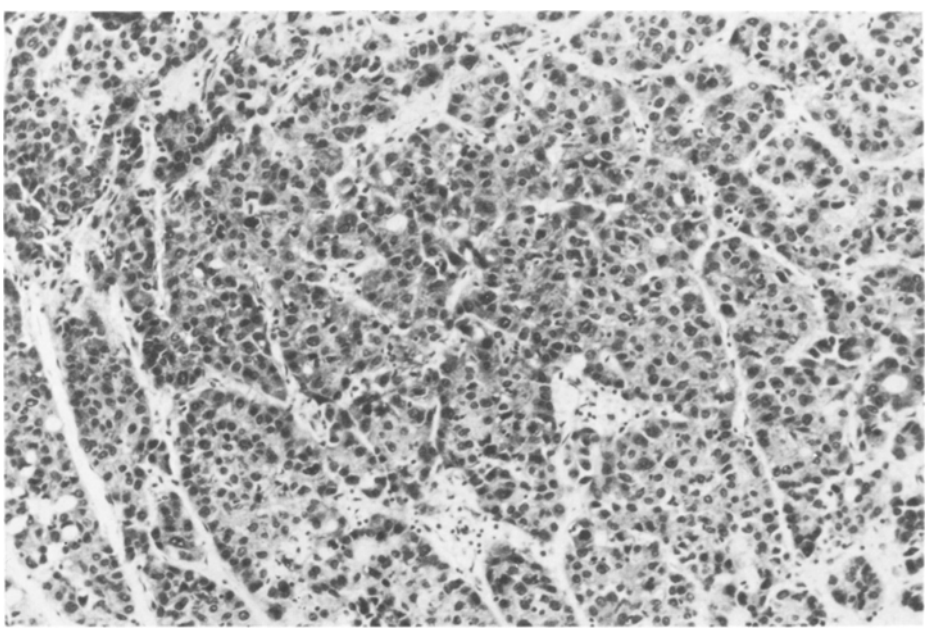

Fig. 4. Histologic section of hepatocellular carcinoma with plump cells in closely packed trabecular configuration. H&E, ×130

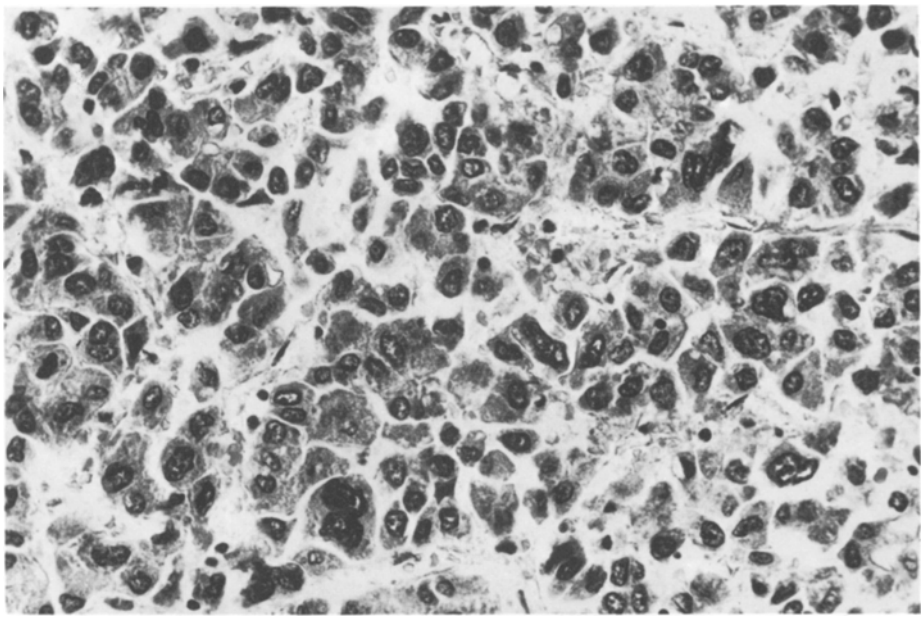

Fig. 5. Higher magnification of hepatocellular carcinoma with extensive cellular and nuclear polymorphism. H&E, ×330

carcinoma cells replacing the original liver tissue were found. The hepatocytes displayed an eosinophilic granular cytoplasm, large nuclei with a heavy nuclear membrane and prominent nucleoli. The cellular and nuclear polymorphism was extensive (Fig. 5). Mitoses were frequent. Fat storage in excess and bile plugs were occasionally observed. Thrombosis due to infiltration of the wall of the portal vein by carcinoma cells was found. The liver capsule showed focal infiltration by carcinoma cells in several areas. Those parts of the liver tissue not involved by carcinoma showed septal and portal fibrosis. Adjacent portal tracts were connected by loose connective tissue bands featuring perilobular fibrosis. The capsule of the liver displayed focal thickening and fibrosis. The areas of fibrosis often extended into the subcapsular liver tissue. Shikata's orcein stain for hepatitis B antigen was negative. The spleen was enlarged, weighing 360 g. On microscopic examination it showed small follicles with germinal centers and moderately dilated red-pulp sinuses with slight fibrosis. Further findings included hemorrhagic diathesis and chronic, inactive tuberculosis of the upper lobe of the right lung.

Discussion

As early as 1961 Torkelson et al. reported liver damage in laboratory animals due to repeated exposure to VC. The oncogenic properties of VC were described in 1971 by Viola et al. but the relationship between VC exposure and human

hemangiosarcoma of the liver did not receive attention before Creech and Johnson reported the occurrence of three cases of hemangiosarcoma of the liver among workers at a polyvinylchloride production plant in Louisville (USA) in 1974.

Our case of hemangiosarcoma of the liver (case report 1) was observed a few months after Lange et al. (1974) and Gedigk et al. (1974) reported the first two cases of hemangiosarcoma due to VC in the Federal Republic of Germany. Meanwhile at least six cases have been observed in this country following the data published by Zimmermann and Eck (1975). Furthermore, we received notice of an unpublished case studied by Gössner (1976). The occupational history of our case demonstrates a characteristic exposure to high doses of VC for many years. Clinical data and autopsy findings closely resemble those reported by Block (1974), Lee and Harry (1974), Lange et al. (1974), Makk et al. (1974), Thomas and Popper (1975), Zimmermann and Eck (1975), and Thomas et al. (1975). The carcinogenicity of VC has been confirmed in several animal experiments by Maltoni and Lefemine (1975), Gordon et al. (1975), and Keplinger et al. (1975). Maltoni and Lefemine (1975) found in rats, mice and hamsters, exposed to VC at various concentrations and time intervals, zymbal gland carcinomas, nephroblastomas, angiomas and angiosarcomas, neuroblastomas, hepatomas, skin carcinomas, and mammary carcinomas. The precise mechanism for the oncogenicity and hepatotoxicity of VC is still unknown. Various experimental and clinical observations suggest that VC, or some metabolic derivatives, presumably formed in the liver, effect both the hepatocytes and the sinusoidal lining cells. Actually Maltoni and Lefemine (1975) found, besides angiosarcomas of the liver, well-differentiated hepatomas with metastases to the lung. Popper and Thomas (1975), studying human material, regarded the combination of hepatocellular hyperplasia with sinusoidal dilatation and sarcomatous transformation of the lining cells as a characteristic finding of the early stage of VC-induced angiosarcoma. However, the progression of activated hepatocytes to a primary hepatocellular carcinoma has so far only been suggested in cases with uncertain relation to VC exposure (Popper and Thomas, 1975).

Our second case presents an hepatocellular carcinoma in a worker who was employed in a PVC polymerization plant for many years. His job involved several functions in the plant and he was definitively exposed to intermittent concentrations of VC of 200 ppm for 4 years. Furthermore, during his employment in the plant for 23 years an exposure to ambient levels of VC in the plant area and working environment seems likely as industrial hygiene control was poor before the danger of VC was recognized. In fact, Schweitzer (1975), who studied the balance of material in the PVC production process in several plants, found a material loss of 4–8%. This means that considerable amounts of VC, and to a lesser extent PVC, are discharged in the environment, mainly into the atmosphere as air emission. To date, little epidemiologic data is available on plant workers, and people living near chemical plants, who have been exposed to intermittent and low levels of VC over a prolonged period of time (Tabershaw and Gaffey, 1974; Monson et al., 1974; Veltman et al., 1975; Creech and Makk, 1975; Edmonds et al., 1975). As this data is not conclusive, and definitive

results are still unavailable, the risk due to VC for this group of people can only be surmised.

Our patient had no history of hepatitis and Shikata's orcein stain for hepatitis B antigen was negative. A possible effect of alcohol consumption on the liver was carefully considered and was excluded. The patient received treatment for tuberculosis of the lung on two occasions for several months. It is universally recognized that tuberculostatic drugs can cause hepatitic injury (Schaffner et al., 1974). However, there is no evidence that these drugs cause either portal or septal fibrosis of the liver or malignant transformation of the hepatocytes. So we may assume that the hepatocellular carcinoma in this case is causally related to the patient's exposure to VC.

The interval between the first exposure to VC and the diagnosis of hemangiosarcoma of the liver in the cases reported ranges from 12 to 28 years (Falk et al., 1974). Thus, we have to be aware of the grave possibility that although so far only cases with a short latent interval resulting from a heavy exposure have been observed, an epidemic of further cases with a longer latent interval and from a lower exposure to VC may yet come. Moreover, the effect of VC on the incidence of certain forms of cancer in man other than hemangiosarcoma of the liver is not yet known. Monson et al. (1974) found in a proportional mortality analysis of deceased workers in two plants using VC a 50% excess of deaths due to cancer. The greatest excess was seen in cancer of the liver and biliary tract, lung, and brain. Nicholson et al. (1975), who studied individuals exposed to VC, found, in addition to hemangiosarcomas of the liver, two malignant lymphomas and one glioblastoma and they suggested the possible relationship of these tumors to VC exposure.

Our own report of hemangiosarcoma and hepatocellular carcinoma adds to the awareness and anxiety that further cases of malignant liver diseases are to be expected. It also emphasizes the need for additional epidemiologic studies, and for the surveillance of those individuals who have been exposed to VC in the past.

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Received August 25, 1976