Cirrhosis After Repeated Trichloroethylene and 1,1,1-Trichloroethane Exposure

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Acute hepatotoxicity has been described in patients exposed to either trichloroethylene or 1,1,1-trichloroethane, but there have been no previous reports of chronic liver disease induced by these agents. We describe a patient who developed cirrhosis and portal hypertension after repeated bouts of acute hepatotoxicity caused by trichloroethylene and a final episode of 1,1,1-trichloroethane-induced liver injury.

A wide variety of chlorinated hydrocarbons have been noted to cause hepatotoxicity. Indeed, carbon tetrachloride, a prototype of this group of compounds, is perhaps the most extensively studied of the hepatotoxins (1). Trichloroethylene and 1,1,1-trichloroethane have enjoyed wide use as solvent substitutes for carbon tetrachloride because of their greater margin of safety. However, acute trichloroethylene exposure in industrial accidents (2) or during "sniffing" (3–5) has resulted in acute neurologic, renal, and hepatic toxicity indistinguishable from that seen with carbon tetrachloride. Although acute 1,1,1-trichloroethane intoxication has usually been associated with acute central nervous system depression alone (6), acute hepatotoxicity secondary to this agent has been reported in animal studies (7–9) and in rare case reports on human subjects (6,10).

Although the development of cirrhosis secondary to carbon tetrachloride is well established in animal models (1) and has been reported in human case studies as well (11,12), we are aware of no previous reports of cirrhosis resulting from trichloroethylene or 1,1,1-trichloroethane exposure. Recently we have observed a patient who developed cirrhosis after repeated exposure to these agents.

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Case Report

A 37-yr-old man was admitted to Parkland Memorial Hospital (PMH) on April 17, 1981, for evaluation of jaundice and massive ascites.

From 1972 through 1974 and again from 1977 through January 1980, the patient worked at an industrial facility where boiling trichloroethylene was used to degrease heavy industrial equipment. During the course of his occupation, the patient frequently noted periods of inebriation after he had inhaled trichloroethylene fumes. On one occasion in 1972 and another occasion in 1973, he was inadvertently trapped in a tank containing residual trichloroethylene for periods of 10–30 min. On both occasions the patient required hospitalization for severe confusion, nausea, and vomiting. During both episodes he was anorectic, fatigued, and jaundiced. Each time all of his symptoms resolved before discharge. We have been unable to retrieve the records of these hospitalizations.

On September 14, 1979 the patient was again trapped for 15–20 min in a tank containing residual trichloroethylene. The patient temporarily lost consciousness and then complained of headaches, tinnitis, blurred vision, anorexia. nausea, and vomiting. Throughout the next week the patient continued to be disoriented and confused. He was admitted to a local hospital on September 23rd where he was observed to be icteric. His blood pressure was 210/100, his pulse was 100 beats/min, and the liver edge was palpable 5 cm below the right costal margin. He was described as being disoriented and confused. The remainder of the physical examination was unremarkable.

Laboratory studies disclosed the following values: blood glucose, 134 mg/dl; blood urea nitrogen, 7 mg/dl; serum sodium, 136 mEq/L; serum potassium, 3.7 mEq/L; serum chloride, 96 mEq/L; Pa_{O_2}, 94 mmHg; Pa_{CO_2}, 29.5 mmHg; arterial pH, 7.5; total serum bilirubin, 5.4 mg/dl; serum glutamic oxaloacetic transaminase, 83 U/L; serum alkaline

phosphatase, 149 U/L; and serum amylase, 99 U/L. The results of a complete blood count and urinalysis were normal. Veneral Disease Research Test and tests for hepatitis B surface antigen (HB_sAg) were nonreactive.

The results of chest x-ray, abdominal sonogram, oral cholecystogram, liver–spleen scan, upper gastrointestinal series, and brain scan were all reported to be normal during the course of a 21-day hospitalization. A liver biopsy specimen was not obtained. Before discharge from the hospital, the results of his liver tests and his mental status examination had returned to normal.

The patient returned to the same place of employment for another 3 mo, although he avoided working in close proximity to trichloroethylene. From January 1980 through December 1980, he worked as a farm laborer and welder. He remained well during this time. From January 1981 until April 1981, he worked in the maintenance department of a brick-manufacturing plant. As part of his job he frequently used aerosolized degreasers containing 1,1,1-trichloroethane (Misty Safety Solvent, Aeromist Inc., Marietta, Ga.; Chemscope Spray, Chemscope Corporation, Arlington, Texas] while working in enclosed areas. During this Same time period the patient noted the onset of progressive fatigue, weight loss, anorexia, icterus, and increased abdominal girth. Repeated questioning of the patient and family members elicited a history of absolutely no ethanol ingestion in the preceding 2 yr. Ethanol consumption before this was limited to one or two cans of beer per day. On admission to PMH he was taking spironolactone and multivitamins, but he had not received any other medication. There was no history of parenteral drug use, blood transfusions, or exposure to people with hepatitis. Admission physical examination revealed an alert, cooperative patient with normal vital signs, and icteric sclerae. Abdominal examination revealed marked ascites and a liver span of 15 cm. The spleen was not palpable. The remainder of the examination was unremarkable: WBC, 13,600/mm^3; hemoglobin, 11.8 g/100 mg; mean corpuscular volume, 103.1 μm^3; prothrombin time 15.6 s (nl 11.1 s), blood urea nitrogen, 33 mg/dl; serum creatinine, 1.5 mg/dl; serum albumin, 2.3 g/dl, serum globulin, 3.8 g/dl; total Serum bilirubin, 12.6 mg/dl with a direct reacting fraction of 8.2 mg/dl; serum alkaline phosphatase, 228 U/L (nl <95); serum glutamic oxaloacetic transaminase, 236 U/L (nl <40); serum creatine phosphokinase, 4 U/L [nl <70); testing for hepatitis B surface antigen was negative; serum a-antitrypsin, 520 mg/dl (nl 200–400 mg/dl), serum ceruloplasmin, 37.2 mg/dl (nl 20–60 mg/dl), serum vitamin B_{12}, 1500 pg/ml (nl 170–1000 pg/ml); and serum folic acid, 9.4 ng/ml (nl >2 ng/ml). Antinuclear antibodies and rheumatoid factor were absent. Analysis of the ascitic fluid revealed 1.2 g/dl protein, 101 mg/dl glucose, 40 U/L amylase, and a white blood cell count of 1300/μm^3 (20% neutrophils]. Bacterial, fungal, and mycobacterial cultures of the ascitic fluid were all negative. ^{99m}Technetium-sulfur colloid scan of the liver revealed diffuse poor uptake in the liver with marked shunting to the bone marrow and an enlarged spleen.

The patient was treated with multivitamins, spironolactone (50 mg p.o. q.i.d.), hydrochlorothiazide (50 mg p.o. q.i.d.), and a diet containing 500 mg/day of sodium. He was discharged on this regimen after a 2-wk hospitalization. During the course of outpatient follow-up. progressive improvement in the results of liver tests and resolution of ascites was noted. By May 29.1981, the patient had lost 20 lb, and ascites could no longer be detected on physical examination. Further laboratory studies revealed the following: hemoglobin, 11.5 g/dl with a mean corpuscular volume of 92 μm^3; prothrombin time, 13s (nl 11.1s); serum albumin, 3.4 g/dl; total serum globulin, 4.2 g/dl; total serum bilirubin, 3.4 mg/dl; serum alkaline phosphatase, 75 U/ml; serum glutamic oxaloacetic transaminase, 80 U/L; blood urea nitrogen, 16 mg/dl; and serum creatinine 1.0 mg/dl. The patient was rehospitalized and a percutaneous liver biopsy was performed with a Menghini needle.

Description of Biopsy

The hepatic architecture was distorted by fibrous tissue septa that encircled small regenerative nodules of hepatocytes, producing a pattern of micronodular cirrhosis (Figure 1). There was pseudoduct formation along the margins of the septa but only a minimal infiltration of lymphocytes, histiocytes, and plasma cells (Figure 2). No Mallory's hyalin or ground-glass cells were identified. Fatty metamorphosis was present in only an occasional parenchymal cell.

Over the next 3 mo the patient's liver function tests gradually improved even further; values on August 21, 1981 were: total serum bilirubin, 1.1mg/dl; serum alkaline phosphatase, 90 U/L; serum glutamic oxaloacetic transaminase, 36 U/L; serum albumin, 3.2 g/dl; total serum globulin, 4.3 mg/dl; and prothrombin time, 15.5 s. However, when diuretic therapy was discontinued, the patient's ascites recurred and subsequently proved to be refractory to the reinitiation of these agents. Eventually, placement of a peritoneovenous Storz Denver shunt, (Storz Instrument Co., St. Louis, Mo.) became necessary. Since then, the patient has avoided exposure to any solvents and has remained asymptomatic without evidence of any further exacerbations of his liver disease.

Discussion

The fact that this patient developed chronic liver disease is manifest by the findings from a liver biopsy specimen. We believe that he progressed to hepatic cirrhosis as a direct consequence of repeated exposure to chlorinated hydrocarbons. A thorough review of this patient's history, physical examination, laboratory parameters, and liver histology has failed to reveal any other likely cause of chronic liver disease. Furthermore, his clinical course has many parallels with those previously described in cases of chronic liver disease resulting from such related chlorinated hydrocarbons as carbon tetrachloride (1,11,12), chloroform (1,13), and tetrachloroethane (1,13).

On several occasions the patient suffered the neurologic and hepatic sequelae well described in the

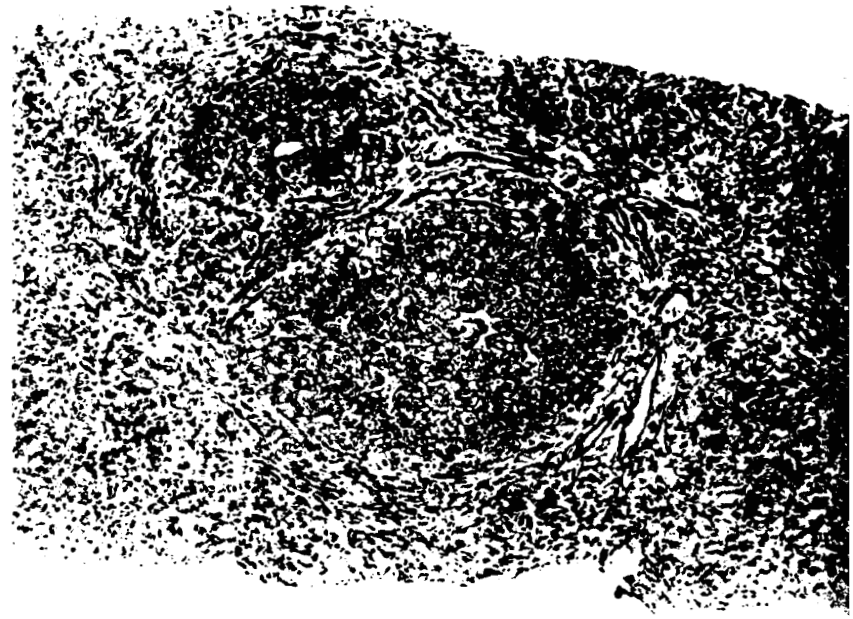

Figure 1. Micronodular cirrhosis in which fibrous tissue septa encircle small regenerating nodules of hepatocytes (H & E; × 50).

setting of acute trichloroethylene intoxication (2–5). He appears to have suffered repeated sublethal but clinically overt episodes of liver injury. This sequence is analogous to the experimental regimens under which carbon tetrachloride has been shown to induce cirrhosis in many species (1). Furthermore, his liver biopsy specimen revealed a cirrhosis with a micronodular pattern similar to that reported in the majority of studies observing carbon tetrachloride-induced chronic liver disease (1). This was not documented, however, until after he had experienced a period of exposure to 1,1,1-trichloroethane. Although the contribution of this exposure to the severity of his chronic liver injury is uncertain, the clinical course suggests that the exposure to 1,1,1-trichloroethane caused additional acute hepatic injury.

In animal studies, acute trichloroethylene exposure has been shown to cause a pattern of centrizonal hepatic steatosis and necrosis typical of that caused by a wide variety of chlorinated hydrocarbons (1,7,8). In case reports of human trichloroethylene intoxication, striking patterns of centrilobular hepatic necrosis have also been observed. Furthermore, 2

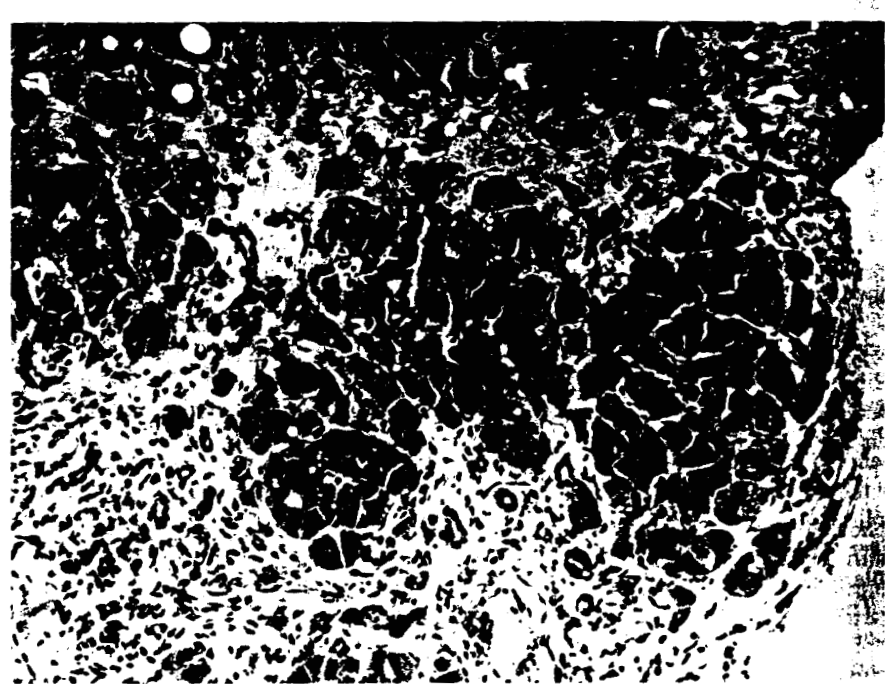

Figure 2. Small clusters of hepatocytes are surrounded by fibrous tissue which consists of mature collagen and is infiltrated by only a scanty number of chronic inflammatory cells (H & E; × 125).

human subjects with a history of multiple exposures to this agent were shown to have centrilobular fibrosis upon examination of a liver biopsy specimen (5).

A pattern of centrizonal steatosis and necrosis of hepatocytes has been observed in an animal study (9) designed to mimic the continuous inhalational exposure to 1,1,1-trichloroethane produced in closed environments and similar to that experienced by this patient. Observers measuring the effects of acute 1,1,1-trichloroethane toxicity in an animal model have documented similar pathological lesions (7). In at least 2 human case reports (6,10), biochemical evidence of hepatotoxicity secondary to acute 1,1,1-trichloroethane exposure was noted though no pathological information was available. The preponderance of evidence suggests that all of the chlorinated hydrocarbons function as direct hepatotoxins (1), probably via the metabolic genesis of active metabolites. It would not be surprising, therefore, if two chemically related compounds such as trichloroethylene and 1,1,1-trichloroethane produced the same toxic metabolite.

We believe that this patient developed hepatic cirrhosis secondary to a combination of repeated trichloroethylene intoxications and a period of exposure to 1,1,1-trichloroethane. This case report therefore lends support to the predictions of previous observers who have suggested that repeated exposure to trichloroethylene might be expected to lead to permanent hepatic alterations (5). In most previous studies, 1,1,1-trichloroethane has proven to be perhaps the least hepatotoxic of the chlorinated hydrocarbons (1,7,8). This case study suggests that an individual suffering previous hepatic injury from a chlorinated hydrocarbon may be at risk for further progression of his disease upon subsequent exposure to even a relatively nontoxic member of this family of organic solvents. We believe therefore that it would be prudent for any patient with evidence of hepatic injury after exposure to one of the chlorinated hydrocarbons to avoid exposure to any other member of this family of commonly used solvents. Because of the structural similarities of these compounds to the halogenated hydrocarbon anesthetics, we believe it would be wise for such a patient to avoid the use of any of these anesthetic gases as well.

References

1. Zimmerman HJ. Direct (toxipathic) hepatotoxins: haloalkanes and elemental phosphorus. In: Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. New York: Appleton–Century Crofts, 1978:198–219.
2. DeFalque RJ. Pharmacology and toxicology of trichloroethylene. A critical review of the world literature. Clin Pharmacol Ther 1960;2:665.
3. Litt IF, Cohen MI. "Danger. . . vapor harmful": spot-remover sniffing. N Engl J Med 1969;281:543.
4. Clearfield HR. Hepatorenal toxicity from sniffing spot-remover (trichloroethylene]. Dig Dis Sci 1970;15:851.
5. Baerg RD, Kimberg DV. Centrilobular hepatic necrosis and acute renal failure in "solvent sniffers." Ann Intern Med 1970;73:713.
6. Stewart RD, Andrews JT. Acute intoxication with methyl chloroform. JAMA 1966;195:904.
7. Plaa GL, Evans EA, Hine CH. Relative hepatotoxicity of seven halogenated hydrocarbons. J Pharmacol Exp Ther 1958; 123:224.
8. Klaassen DC, Plaa GL. Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. Toxicol Appl Pharmacol 1967;10:119.
9. McNutt NS, Amster RL, McConnell EE, Morris F. Hepatic lesions in mice after continuous inhalation exposure to 1,1,1-trichloroethane. Lab Invest 1975;32:642.
10. Nathan AW. Toseland PA. Goodpasteure's syndrome and trichloroethane intoxication. Br J Clin Pharmacol 1979;8:284.
11. Poindexter CA, Greene CH. Toxic cirrhosis of the liver. Report of a case due to long continued exposure to carbon tetrachloride. JAMA 1934;102:2105.
12. Hardin BL Jr. Carbon tetrachloride poisoning—a review. Index Med Surg 1954;23:93.
13. Willcox W. Toxic jaundice. Lancet 1931;ii:57.