TCE - Liver/Kidney

Centrilobular Hepatic Necrosis and Acute Renal Failure in "Solvent Sniffers"

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Three teenagers with a history of drug abuse developed acute hepatic injury after the inhalation of Carbona® cleaning fluid, a commercial preparation that contains trichloroethylene. Two of these patients had evidence of acute renal injury, presumably due to tubular necrosis. Electrocardiographic and electroencephalographic abnormalities were also noted. Hepatic biopsies in two patients showed acute centrilobular necrosis. Both biopsies also showed evidence of mild centrilobular fibrosis, probably a result of previous injury from exposure to trichloroethylene. Carbona "sniffing" seems to be increasingly popular among adolescents, and its use in a group that has abused other drugs complicates an already difficult situation.

TRICHLOROETHYLENE is a chlorinated hydrocarbon ($CHCl=CCl_2$) with wide industrial and limited medical application. Its low volatility, noninflammability, and poor water solubility make it a useful solvent for degreasing metals, dry cleaning, and for fat extraction. It is also used in paints, lacquers, adhesives, and in silicone parting agents. Medically its use (Trilene®, Great Britain; Trethylene®, United States) is currently limited to anesthesia and analgesia, particularly in obstetrics, where it has been used as a 0.5% mixture with air. The agent has a history of a variety of other medical uses, including the treatment of angina pectoris, trigeminal neuralgia, and emotional disorders and as a wound cleanser and an antihelminthic. These uses have been abandoned as ineffective.

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In addition to these uses, Carbona® cleaning fluid (currently a solution of 44% trichloroethylene and 56% by volume petroleum distillates) and Carbona Number 10 Special Spot Remover® (currently containing 40% trichloroethylene, 10% 1,1,1-trichloroethane, and 50% by volume petroleum distillates) have recently been popular among "solvent sniffers." The acute and chronic toxic effects of trichloroethylene have been incompletely appreciated in "solvent sniffers" in this country (1), despite many reports on the hazards of industrial inhalation. Recent reviews provide a more complete understanding of the subject (2, 3).

Two patients with acute hepatic and renal damage and another with centrilobular hepatic necrosis attributable to Carbona cleaning fluid* "sniffing" are described.

Case Reports

CASE 1

Patient T.M., a 15-year-old white boy, was admitted to Presbyterian Hospital, New York, on 18 September 1968 because of icterus. Except for drug abuse, he had been in good health. He had had regular exposure to a variety of model airplane glues, amphetamines, heroin, cocaine, and marijuana. He denied the parenteral administration of drugs, and he did not consume alcoholic beverages. He had "sniffed" Carbona cleaning fluid on one occasion 10 months before admission, after which he noted severe headache. In the month before admission he "sniffed" glue occasionally but used none of the other agents. Six days before admission Carbona cleaning fluid was inhaled, causing drowsiness. This was repeated the following day, after which headache, anorexia, and vomiting appeared. The next day the fumes were again inhaled, and later the same day he noted a sore throat, fever, and chills. The following day, 3 days before admission, he was jaundiced and had dark urine.

* In Cases 1 and 2 the patients inhaled an older solution of Carbona which contained 70% trichloroethylene and 30% by volume petroleum distillates.

Two days later, on 17 September 1968, the patient was seen at the Columbia-Presbyterian Medical Center where icterus was confirmed. On admission to the hospital the following day, the patient's vital signs were normal. No rash was present. The liver was slightly tender, and its edge was palpable 3 cm below the right costal margin; the spleen tip could also be palpated. The rest of the physical examination, including the neurological examination, was within normal limits.

Pertinent laboratory tests of hepatic function are summarized in Table 1. Other significant laboratory tests on admission included a hemoglobin of 14.2 g/100 ml; WBC count, 6,160/mm³ with 50% neutrophils, 33% lymphocytes, 8% monocytes, 8% eosinophils, and 1% basophils. A subsequent WBC and differential count on the twelfth hospital day was entirely normal, with 1% eosinophils. A platelet count was 260,000/mm³, and the erythrocyte sedimentation rate (Wintrobe method) was 26 mm in 1 hr. The urinalysis on admission showed a specific gravity of 1.005, pH 6.0, no protein or glucose, and a negative microscopic examination. Urinalysis on the fifth hospital day showed a specific gravity of 1.025, pH 5.0, 1+ protein, no glucose, one to two WBC/hpf, and occasional finely granular casts. No additional urinalyses were recorded. Blood urea nitrogen (BUN) was 15 mg/100 ml. Serum albumin was 4.4 g/100 ml; and serum globulin, 2.6 g/100 ml. An electrocardiogram on admission showed T-wave inversion in V_{2-3} and T-wave lowering in V_{4-6}; subsequent electrocardiograms were normal.

The patient became asymptomatic shortly after admission. Tests of hepatic function were initially abnormal but rapidly returned to normal (Table 1). Serum glutamic-oxalacetic transaminase (SGOT) was normal by the sixth hospital day, whereas serum glutamic-pyruvic transaminase (SGPT) returned to normal more slowly.

Six days after admission a percutaneous liver biopsy was performed with a Menghini needle. Microscopic examination of the tissue (Figures 1 and 2) showed extensive hepatocellular necrosis with collapse of the reticulin framework, largely restricted to central areas. In these areas hepatocytes were notably absent, and there was preservation of the sinusoidal architecture. There was a moderate mononuclear cell infiltrate in the central areas. Mild centrilobular fibrosis, confirmed by trichrome stains, was present in a few regions. The portal areas were entirely normal, and the lobular architectural pattern was not disturbed. Biopsy showed acute toxic centrilobular necrosis superimposed upon a previous centrilobular injury.

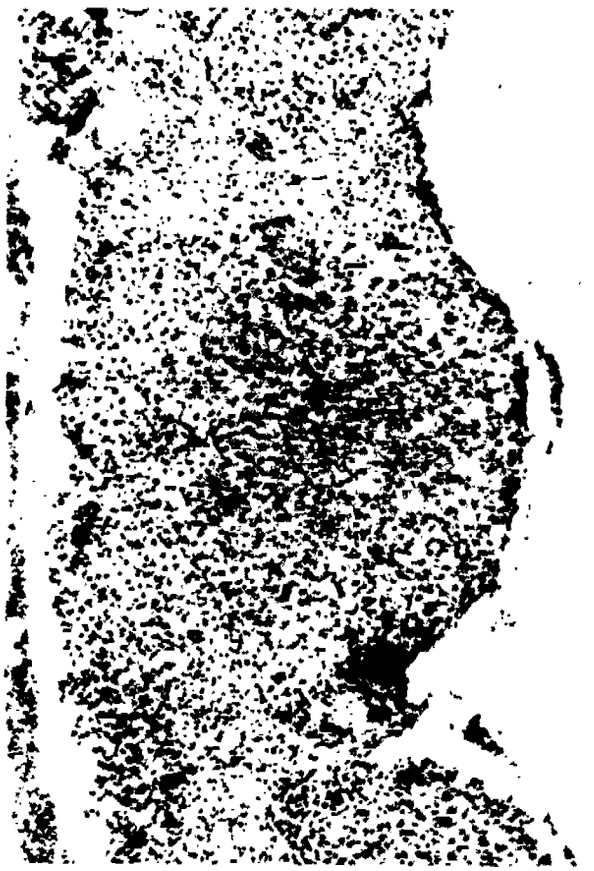

Figure 1. Biopsy of the liver of Patient 1, 12 days after the onset of the most recent episode of Carbona "sniffing" and 6 days after admission to the hospital. See text for description. (Hematoxylin and eosin; original magnification, × 25.2, × 2.5.)

The patient had an uneventful recovery and was discharged on the thirteenth hospital day. The only medication given was a standard multivitamin preparation. Two weeks after the patient was discharged his SGOT, SGPT, and alkaline phosphatase were normal. He continues to use marijuana but has avoided other agents.

CASE 2

Patient D.S., a 15-year-old white girl, was admitted to Presbyterian Hospital on 8 August 1967 because of anuria of 3 days' duration. Her pertinent medical history included an uncomplicated tonsillectomy and adenoid-

Table 1. Hepatic Function Tests in Patient 1

Hospital Day	Serum Glutamic-Oxalacetic Transaminase*	Serum Glutamic-Pyruvic Transaminase*	Alkaline Phosphatase†	Bilirubin		Prothrombin Time	
				Direct	Total	Patient	Control
				mg/100 ml		*sec*	
−1	3,800	3,100	34	1.07	3.12	16	13
2	200	890	28	0.43	1.18	—	—
6	50	245	—	—	—	14	13
7	40	200	—	0.19	0.64	—	—
13	33	70	15	0.15	0.31	—	—

* Modified Karmen units, normal, 10 to 40 units.
† King-Armstrong units; normal, 10 to 15 units.

ectomy with cyclopropane anesthesia at age 5 years. Urinalysis at that time showed a specific gravity of 1.024, pH 5.5, and two to three WBC/hpf. A routine urinalysis 3 years before the present illness was also normal.

Eighteen months before admission the patient began "sniffing" glue to the point of inebriation two to five times weekly, a practice that was discontinued 6 weeks before admission. At that time she began to ingest various amphetamines and barbiturates but did not consume alcoholic beverages. Five weeks before admission she intentionally lacerated her left wrist with a razor blade. Approximately 1 week later she began to "sniff" Carbona cleaning fluid every other day, and 1 week before admission she began to inhale it nightly, despite tearing, rhinorrhea, and a bifrontal headache. Three days before admission, nausea, vomiting, and right upper quadrant pain appeared and persisted; the pain became worse with movement. She also noted the absence of urine. The day before admission she had alternating chills and fever.

At admission her temperature was 100 F, rectally; pulse, 120/min; and blood pressure, 114/60 mm Hg. No rash, petechiae, or icterus was evident. The pharynx was erythematous, but no exudate was observed. Bilateral costovertebral angle tenderness on percussion and right upper quadrant tenderness on palpation were noted. The liver, spleen, and kidneys were not palpable. The rest of the physical examination, including the neurological examination, was normal.

Laboratory studies on admission were as follows: hemoglobin, 14.3 g/100 ml; WBC count, 13,200/mm^3 with 84% neutrophils, 11% lymphocytes, 3% monocytes, and 2% eosinophils. The erythrocyte sedimentation rate (Wintrobe method) was 6 mm in 1 hr. Urinalysis showed a specific gravity of 1.010, pH 5.0, 3+ protein, O-trace glucose, two to four WBC/hpf, and many RBCs. The serum albumin was 4.3 g/100 ml and serum globulin, 2.1 g/100 ml. An ECG and tests for blood sugar and serum calcium were normal. Alkaline phosphatase was 11 King-Armstrong units. Serial determinations of other tests of hepatic and renal function are summarized in Table 2.

The clinical impression was that the patient had acute tubular necrosis and toxic hepatitis, both secondary to Carbona "sniffing." She was treated with bed rest, a low protein diet (20 g/day), sodium and fluid restriction, and parenteral vitamin K for correction of the abnormal prothrombin time. As shown in Table 2, the SGOT, bilirubin, and prothrombin time returned to normal within her first 9 days in the hospital. On the twentieth hospital day there was 7% retention of sulfobromophthalein (BSP) 30 min after intravenous injection of 5 mg/kg body weight.

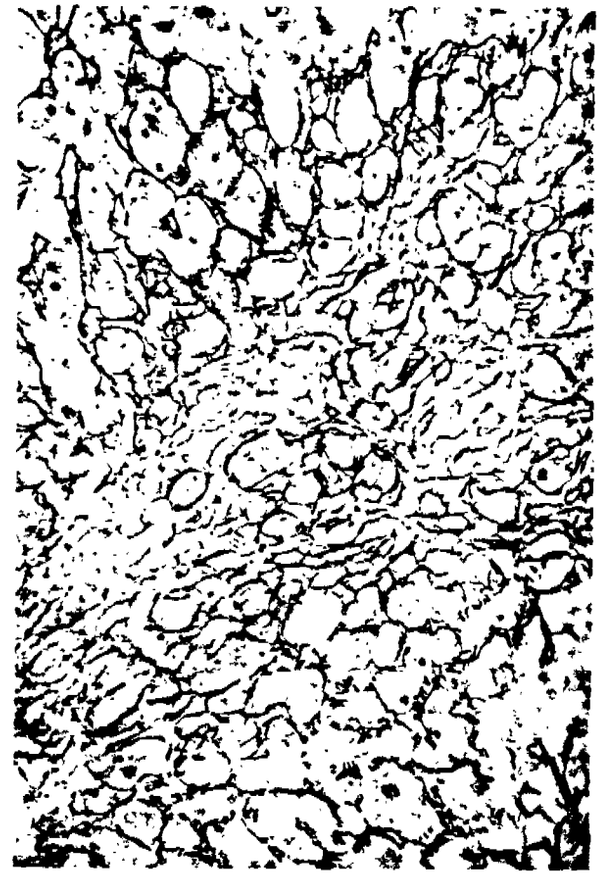

Figure 2. Biopsy of the liver of Patient 1. See text for description. (Laidlaw *reticulin stain; original magnification,* × 64, × 2.5.)

Oliguria with a daily urine output in the range of 250 to 328 ml persisted until the fifth hospital day, at which time the urine volume rose to 585 ml/24 hr and the BUN had reached 87 mg/100 ml. Urine volume continued to rise and reached a peak of 2,630 ml/24 hr on the eleventh hospital day. Thereafter, the volume decreased to normal, and the patient was discharged on the twentieth hospital day with a BUN of 18 mg/100 ml. A urinalysis on the fourth hospital day showed a specific gravity of 1.008, pH 8.0, 2+ protein, no glucose, five

Table 2. Hepatic and Renal Function Tests in Patient 2

Hospital Day	Serum Glutamic-Oxalacetic Transaminase*	Serum Glutamic-Pyruvic Transaminase*	Bilirubin		Prothrombin Time		Blood Urea Nitrogen
			Direct	Total	Patient	Control	
			mg/100 ml		*sec*		*mg/100 ml*
1	2,300	—	0.7	2.1	24	13	33
7	29	90	—	1.0	15	14	78
10	25	43	—	—	15	14	87
16	45	20	—	—	—	—	24
20	—	—	—	—	—	—	18

* Modified Karmen units; normal, 10 to 40 units.

to seven RBCs/hpf, and many WBCs. No subsequent urinalyses were recorded.

Despite psychotherapy since discharge, she has continued to use marijuana, phenothiazines, barbiturates, and heroin. When seen 12 months after discharge she had shared needles with jaundiced addicts and was noted to be icteric and to have tender hepatomegaly. Hospitalization at that time was declined by the patient. No further follow-up information is available.

CASE 3

Patient S.H., an 18-year-old white man, was admitted to Presbyterian Hospital on 16 March 1970 because of of abdominal pain of 5 days' duration. He was examined at age 12 because of a behavioral disorder and was said to have a passive-aggressive personality. A urinalysis, urine culture, and intravenous pyelogram were done at age 13 because of enuresis, and all of these tests were normal.

He began "sniffing" Carbona cleaning fluid at age 15, using approximately 4 oz daily for several days in succession. Drowsiness and nightmares were the only symptoms noted. In August 1969 he smoked marijuana, ingested barbiturates, and injected LSD and heroin intravenously. In October 1969 he inhaled 4 oz of Carbona cleaning fluid daily for 2 weeks, stopped for several days, and then began using up to 8 oz daily. He accidentally ingested an unknown quantity of this agent and was treated with gastric lavage at another hospital. He noted no symptoms other than drowsiness after the ingestion. In November 1969 Carbona cleaning fluid was again "sniffed" daily, but this was discontinued shortly before an admission to Presbyterian Hospital on 16 November 1969 for removal of pilonidal cysts. The only symptom related to trichloroethylene toxicity at that time was vague abdominal pain during the week before admission.

Physical examination in November 1969 showed a blood pressure of 146/90 mm Hg and multiple pilonidal cysts and sinuses. The examination was otherwise normal. Laboratory tests included a hematocrit of 50% and a WBC count of 7,100/mm^3 with 4% eosinophils. A urinalysis was normal, and the BUN was 16 mg/100 ml. Tests of hepatic function were abnormal. The total bilirubin was 1.2 mg/100 ml; SGOT was 670 I.U. (normal, 10 to 50); lactic dehydrogenase, 270 I.U. (normal, 90 to 200); alkaline phosphatase, 80 I.U. (normal, 30 to 85); serum albumin, 4.1 g/100 ml; and globulin, 3.0 g/100 ml. On the third hospital day the patient's temperature rose to 101 F, surgery was postponed, and he was subsequently discharged from the hospital to be followed in the medical clinic.

After discharge from the hospital he refrained from using all parenteral agents but was lost to medical follow-up until his second admission. Between 6 March and 10 March 1970 the patient "sniffed" 4 oz of Carbona cleaning fluid daily. On 7 March he ingested one capsule containing an amphetamine. On 11 March, 5 days before admission, he noted malaise and dull, steady, midabdominal pain. The pain persisted, and the following day it was accompanied by nausea and vomiting. On 13 March he was seen at the Columbia-Presbyterian Medical Center Emergency Room, where his physical examination was normal. Hemoglobin, WBC count, and differential count were also normal. Urinalysis showed a specific gravity of 1.015, 2+ protein, and one to two RBCs/hpf. No WBCs or casts were seen. He was sent home but returned 3 days later, still complaining of nausea, and was admitted to the hospital. He denied headache, urinary symptoms, fever or chills.

Physical examination showed a blood pressure of 150/100 mm Hg. Other vital signs were normal. The sclerae were icteric; the liver, kidneys, and spleen were not palpable, but there was mild tenderness on percussion of the right upper quadrant of the abdomen. The neurological examination was normal.

Laboratory tests showed: hematocrit, 43%; WBC count, 4,100/mm^3 with a normal differential; the initial urinalysis showed a specific gravity of 1.020, no protein and one to three WBCs, four to five RBCs, and occasional granular casts/hpf. Subsequent urinalyses showed a specific gravity of 1.017 to 1.020 and up to 20 RBCs and 8 WBCs/hpf. Hyaline and finely and coarsely granular casts were variably present, and 2+ proteinuria reappeared transiently on the tenth hospital day. The urinalysis was entirely normal on the fifteenth hospital day. Serum albumin was 4.2 g/100 ml and globulin, 2.6 g/100 ml. The prothrombin time was 13 sec (control, 12 sec). When tested in the laboratory of Dr. David Gocke, the serum did not contain the hepatitis antigen. The results of other tests of renal and hepatic function are summarized in Table 3. An ECG and serum calcium and phosphorus were normal. An electroencephalogram done on the fourth hospital day was

Table 3. Hepatic and Renal Function Tests in Patient 3

Hospital Day	Serum Glutamic-Oxalacetic Transaminase*	Serum Glutamic-Pyruvic Transaminase*	Lactic Dehydrogenase†	Alkaline Phosphatase‡	Bilirubin		Blood Urea Nitrogen	Serum Creatinine
					Direct	Total		
					← mg 100 ml →			
−3	6,120	—	4,620	90	—	4.00	19	—
2	460	—	70	69	—	2.00	37	1.6
4	142	848	—	74	0.62	1.39	26	1.4
8	63	374	—	85	0.41	0.93	21	1.2
12	50	168	—	52	0.39	0.77	24	1.2
15	34	74	—	—	0.33	0.59	19	1.1
17	29	58	—	46	0.36	0.61	21	1.2

* International Units; normal, 10 to 50 units
† International Units; normal, 90 to 200 units.
‡ International Units; normal, 30 to 85 units.

normal at rest, but bursts of medium to high voltage 1½ to 3/sec waves were seen bifrontally during hyperventilation. A liver biopsy with a Menghini needle was also done on the fourth hospital day. Microscopic examination of the tissue (Figures 3 and 4) showed extensive centrilobular necrosis with collapse of the reticulin framework. A mild polymorphonuclear leukocyte inflammatory reaction was associated with the necrotic areas. The sinusoidal architecture was not disturbed. Although a moderate amount of fibrous tissue was seen in many central areas, the portal areas were quite normal. The biopsy was interpreted as showing acute toxic hepatitis with an older, healed centrilobular lesion, probably the result of previous halogenated hydrocarbon injury.

The patient was treated only with bed rest and had an uneventful recovery. On the seventeenth hospital day the BUN was 21 mg/100 ml, and the serum creatinine had fallen to 1.2 mg/100 ml. On the eighteenth hospital day the BSP retention was 7% 30 min after the injection of 5 mg/kg body weight, and the patient was discharged from the hospital.

Discussion

These patients are presented in detail to illustrate the clinical presentation of individuals with acute trichloroethylene inhalation toxicity and to alert physicians who have contact with "solvent sniffers" to the possible toxic effects of this agent.

Figure 3. Biopsy of the liver of Patient 3, 14 days after the onset of the most recent episode of Carbona "*sniffing*" and 4 days after admission to the hospital. See text for description. (Mallory trichrome stain; original magnification, × 25.2, × 2.5.)

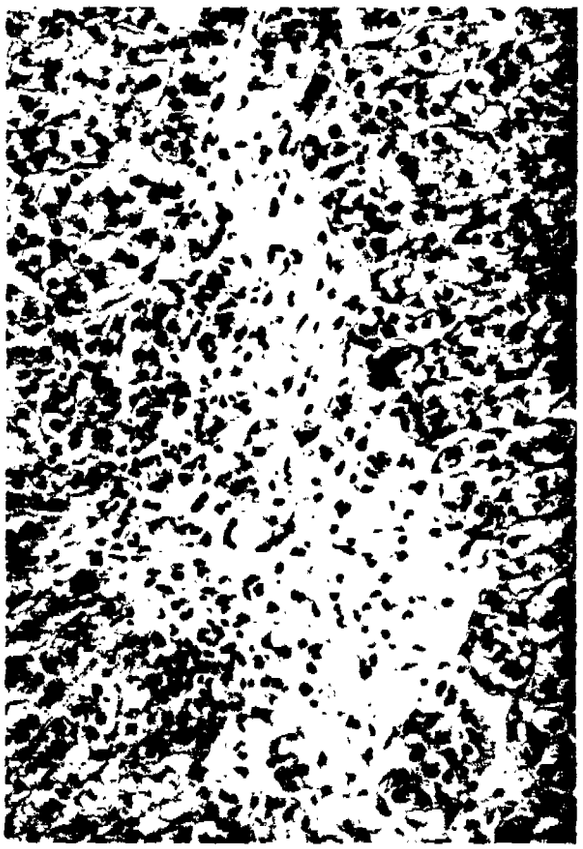

Figure 4. Biopsy of the liver of Patient 3. See text for description. (Heamtoxylin and eosin stain; original magnification, × 64, × 2.5.)

Experimental inhalation of trichloroethylene results in an estimated 51 to 70% retention of the agent by the lungs (4, 5). The exact fate of the retained trichloroethylene is unclear (3), but approximately 70% (4) is metabolized to a variety of substances that are recoverable in the urine. These include trichloroacetic acid (10 to 36%) (4, 5), trichloroethanol (32 to 59%) (4, 5), and monochloroacetic acid (4%) (4). Small amounts of trichloroacetic acid and trichloroethanol are also excreted in sweat, saliva, and feces (5). The remaining trichloroethylene is excreted unchanged by the lungs within 48 hr, and only small amounts of the unaltered agent are found in the urine (5). It is still unclear whether trichloroethylene per se or one of its metabolites is responsible for toxicity. Evidence favors trichloroethanol as the most toxic agent, particularly for the central nervous and cardiac conduction systems (6), although monochloroacetic acid has been implicated because of its ability to inhibit various enzyme systems (5).

A discussion of the toxicity of trichloroethylene inhalation is properly separated into two exposure situations: [1] chronic industrial exposure to low concentrations and [2] acute or recurrent massive inhalation, as occurs in industrial accidents, trichloroethylene anesthesia, and exposure incurred by "solvent sniffing." Chronic exposure in metal degreasers has been reported to result primarily in a neuropsychiatric symptom complex consisting of tremors, giddiness, alcohol intolerance, a neurasthenic syndrome with anxiety states, and bradycardia, as well as increased lacrimation, reddening of the skin, decreased sensitivity of the hands, and insomnia (7). In rats, prolonged trichloroethylene inhalation produces neuromuscular depression and possibly a reduction in fear inhibition (8).

None of the recent industrial surveys have confirmed the presence of retrobulbar neuritis described earlier (3), although anesthesia of trigeminal nerve endings has been noted (7). Despite this report, the use, so popular at the beginning of the century, of trichloroethylene in the treatment of trigeminal neuralgia has largely been abandoned. This is in part owing to the variable clinical response, particularly in patients with chronic symptoms, and to studies that showed that the effects of trichloroethylene inhalation were a nonspecific result of general anesthesia or sedation (9). Anosmia with presumed olfactory nerve damage has also been reported (10). Anorexia and other functional gastrointestinal complaints have been considered to be manifestations of chronic toxicity; although the cause is unclear, the gastrointestinal disturbances have been attributed to autonomic nervous system dysfunction (11).

Other manifestations of chronic industrial trichloroethylene inhalation have been even less well defined and are described primarily in case reports. Severe hepatic damage is decidedly unusual, but fatal hepatic necrosis has been reported after chronic industrial exposure (12). Abnormalities of hepatic function have been noted by various workers (3), and it has been shown that elevations of serum glutamic-oxalacetic transaminase (SGOT) and aldolase may be potentiated by pretreatment with ethanol (13). This effect of ethanol has been confirmed experimentally in rats (14). Chronic exposure of a variety of experimental animals to trichloroethylene inhalation has produced neither significant dysfunction nor abnormal hepatic histology (15).

The important acute effects of massive trichloroethylene inhalation are usually those related to central nervous system depression. The cardinal manifestation of such exposure is a depressed level of consciousness that may be preceded by either mild excitation or euphoria. The usual postrecovery symptom is headache (16), a symptom experienced by two of the patients in this report. Organic cerebral and cerebellar dysfunction has also been noted (7). The electroencephalographic changes occurring after industrial accidents (17) have also been noted in guinea pigs given trichloroethylene and trichloroethanol intraperitoneally (6). It has been found that trichloroethanol is three times more effective than trichloroethylene in reducing cerebral cortical electrical excitability and in causing both electroencephalographic and electrocardiographic abnormalities (6).

Another potential hazard of acute trichloroethylene inhalation is the occurrence of cardiac arrhythmias. Atrial flutter with atrioventricular block, nodal rhythm, multifocal premature ventricular contractions, ventricular tachycardia (18), and ventricular fibrillation (19) have been seen during trichloroethylene anesthesia or analgesia in humans. Orth and Gillespie (20) noted significant changes in rhythm or rate in 13 of 14 patients anesthetized with this agent, and others (21) have noted similar abnormalities in 33 of 40 patients, with a 10% frequency of multifocal ventricular tachycardia. Ventricular fibrillation has been considered the cause of death in cases of industrial inhalation (22, 23) and may have played a role in the deaths of three "sniffers" (24). Respiratory insufficiency with tachypnea, perhaps secondary to an augmented sensitivity of pulmonary stretch receptors (3), may also have contributed to these fatalities. The transient electrocardiographic abnormality consisting of precordial T-wave inversion in Case 1 has been noted previously (25).

Renal damage, such as that noted in Cases 2 and 3, is more unusual than hepatic toxicity. Postanesthesia urinalyses in patients who had received trichloroethylene have not indicated the presence of renal injury (2, 3); however, one of Cotter's (16) patients with acute massive inhalation had a urinalysis suggestive of acute tubular necrosis. Furthermore, Gutch, Tomhave, and Stevens (25) reported a patient with acute tubular degeneration documented by renal biopsy. Acute renal failure requiring dialysis has also been seen by Litt and Cohen (1) in "solvent sniffers."

The effects of experimental inhalation in animals on renal and hepatic function have been variable, perhaps reflecting substantial differences in the species used and in the experimental technique. Although trichloroethylene inhalation has been reported to cause toxic nephritis in rodents after acute exposure (2), no histologic evidence of renal damage has been seen in a variety of animals used in other studies (15). Urea clearance is normal in dogs sub-

jected to repeated trichloroethylene anesthesia (20).

Fatal hepatic necrosis has been reported in association with massive industrial exposure (26) and has also been noted after trichloroethylene anesthesia (2, 3, 27-30). In the latter instance the association has often been obscured by severe intercurrent illness. Under usual anesthetic circumstances tests of liver function are either unchanged or are only mildly and transiently abnormal (2). Although acute exposure in dogs affected neither sulfobromophthalein retention nor hepatic histology (2, 3), subacute exposure caused pronounced abnormalities in both aspects (20).

Abnormal tests of hepatic function (1) or abnormal hepatic histology (10) have been seen only rarely in "solvent sniffers." All three patients described in the present report had SGOT and serum glutamic-pyruvic transaminase values and a clinical history consistent with an acute toxic hepatitis. In Cases 1 and 3 the liver biopsy demonstrated centrilobular necrosis, a finding characteristic of chlorinated hydrocarbon hepatotoxicity. The presence of fibrous tissue in the centrilobular zones of the biopsies in both cases suggests that repeated exposure may produce permanent hepatic alterations, but the functional significance, if any, of such lesions remains obscure. The predominantly centrilobular location of the lesion in the patients with trichloroethylene and other chlorinated hydrocarbon toxicity may reflect alterations in the intralobular circulation (31), differing susceptibility of cells in different lobular areas, or zonal differences in the intracellular concentration of the hepatotoxins (32).

Although little is known concerning the biochemical effects of trichloroethylene or its metabolites on hepatic cell metabolism, there has been a great deal of interest in elucidating the mechanism underlying the toxic action of carbon tetrachloride. It is not unlikely, however, that the hepatotoxic effects of these related chlorinated hydrocarbons are mediated by a similar chain of events. Several mechanisms have been considered to account for the effects of carbon tetrachloride, but precise definition of the initiating biochemical event remains uncertain. This has been the subject of a recent extensive review (32).

Carbon tetrachloride causes profound alterations in the mitochondria of hepatic cells, with evidence of swelling, altered permeability, an increase in calcium content, a loss of nicotinamide adenine dinucleotide (NAD), a decrease in the activity of NAD-linked tricarboxylic acid cycle dehydrogenases, a fall in adenosine triphosphate levels, and uncoupling of oxidative phosphorylation. It seems unlikely, however, that mitochondrial injury represents the initial event. Recent studies with carbon tetrachloride have suggested that there is an earlier effect on the endoplasmic reticulum, leading to inhibition of protein synthesis, impaired lipoprotein synthesis, lipid accumulation, and ultimate cell necrosis. This damage to the endoplasmic reticulum may be due to carbon-tetrachloride-related peroxidation of structural lipids (32, 33). Other recent studies (34) have suggested that carbon-tetrachloride-induced lysosomal rupture leading to an early disruption of protein synthesis may be the initiating event in the hepatic injury.

Unfortunately, the therapy for trichloroethylene inhalation excess has been less well evaluated than the toxic manifestations (3). Measures such as withdrawal of the agent, avoidance of ethanol, and the management of acute hepatic or renal failure, or both, seem obvious. The use of tetraethylthiuram disulfide (disulfiram) has been suggested, especially in those who have ingested trichloroethylene (35). This compound appears to inhibit the formation of trichloroacetic acid and trichloroethanol from trichloroethylene, and its administration is associated with an enhancement of the pulmonary excretion of trichloroethylene. The use of such agents is probably best deferred, however, until more evidence is available concerning the identity of the hepatotoxic and nephrotoxic metabolite. While antioxidants such as alpha-tocopherol may protect against carbon tetrachloride damage in experimental animals (32), the clinical applicability, if any, of this observation is unknown.

Trichloroethylene has a sweet smell, and its inhalation may produce a sense of elation. It has been suggested that addiction to the inhalation of this agent may occur (3). Carbona "sniffing" seems to be increasingly popular among adolescents, and its use in a group that has abused other drugs can complicate an already difficult situation. Unless the exposure is recognized, a mistaken diagnosis of viral hepatitis may be made. A history of "solvent sniffing," the acute onset of symptoms, the possible accompaniment by evidence of renal damage, the absence of the so-called hepatitis antigen, and the relatively rapid resolution of the signs of hepatic injury should help distinguish toxic hepatitis from that owing to viral infection. The complete absence of portal inflammation and the centrilobular location of the damage seen on biopsy of these patients leaves little doubt that they had toxic rather than viral hepatitis. The presence of centrilobular scarring in both biopsy specimens suggests that repeated exposure may lead to permanent hepatic alterations, but the functional significance of such lesions is unknown.

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