UNUSUAL SPLENOMEGALIC LIVER DISEASE AS EVIDENCED BY PERITONEOSCOPY AND GUIDED LIVER BIOPSY AMONG POLYVINYL CHLORIDE PRODUCTION WORKERS

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INTRODUCTION

Economic Considerations; Technology

As early as 1833[1] and 1838,[2] respectively, Regnault in France succeeded in preparing vinyl chloride (VC) and polyvinyl chloride (PVC). However, the road to large-scale production was not opened until vinyl chloride could be synthesized from acetylene and hydrogen chloride (Klatte and Zacharias, 1912)[3,4] and organic peroxides were used for catalyzing VC polymerization (Klatte and Rollett, 1914).[5] In 1928, PVC production was started in the United States and in 1933 in Germany.[6] The enormous growth of VC and PVC production capacities over the past 45 years ran parallel to the rising economic importance of plastic materials[7] (TABLE 1).

PVC-producing industries in West Germany increased their production, parallel to the development in the United States (TABLE 2), at a rate of 10–20 percent per year from 1960 (172,673 tons of PVC) to 1972 (930,701 tons of PVC and polyvinylidene chloride).[8,9] Total sales of PVC amounted to 850,140 German marks in 1972.[10] This enormous increase in production capacity, especially in flexible PVC (U.S., 1965: flexible PVC, 90 percent; rigid PVC, 10 percent)[4] can be explained by the almost unlimited use that can be made of PVC. Diversification of PVC markets exceeds that of any other large-volume thermoplastic and is one of the reasons for the increasingly favorable market situation (TABLE 3).[11]

Rigid PVC is used for tubing and fittings (including insulation material and drainage pipes), foils, films, and sheeting (packaging, lining, recording tapes), profiles (blinds, window frames), tiles, sound records, and fibers. *Flexible PVC* is used for cables, foils (decoration, roof covering), profiles, tubing, artificial leather, flooring, foam rubber, paint, varnish (lacquer), and toys.[12] Thus, industries that manufacture the end product operate on a much larger scale than those producing the polymer, but the companies are often identical.[13,14]

Technologically, vinyl chloride was synthesized mainly by hydrochlorination of acetylene, a process which was almost exclusively in operation up to 1960, but in the United States now accounts for only 7 percent of the production.[15] Vinyl chloride can also be produced by oxychlorination of ethylene to 1,2-dichloroethane which is then cracked to VC and HCl by subsequent pyrolysis (now 93 percent of total production in the United States in 1972).[4,6,8,15,16] Under

TABLE 1
WORLD PRODUCTION OF PLASTICS IN MILLION TONS PER YEAR[44]

Year	Million Tons
1930	<0.1
1950	1.5
1960	6.9
1970	30.0

TABLE 2
WORLD PRODUCTION AND PRODUCTION CAPACITY FOR PVC RESINS (MILLION TONS)[37,38,65]

	Production			Annual Capacity		
	1950	1960	1972	1960	1972*	1975*
Western Europe	0.053	0.578	2.948	0.583	3.583	
Western Germany	0.014	0.173	0.930	0.195		
United States			1.950	0.610	1.995	3.175
Japan			1.088	0.270	1.587	
Eastern Europe			0.861	Not stated	0.816	
Other areas			0.544	0.152	0.816	
Total			7.391	1.615	8.797	

* Estimated capacities.

TABLE 3
DIVERSIFICATION OF PVC MARKETS[114]

PVC Market	Consumption (%)
Calendering	18
Extruded products	14
Wire and cable	12
Calendered flooring	10
Film and sheet	6
Paper and textile coating	5
Sound records	5
Plastisols	5
Protective coatings and adhesives	4
Injection and blow molding	3
Coated flooring	2
Other domestic uses	11
Exports	5

ambient conditions, vinyl chloride (CH=CHCl, mol.wt. = 62.5)[66] is a colorless inflammable gas of faintly sweet odor. At −13.8°C and 760 torr it condenses to a colorless liquid of low viscosity.[66] VC reactivity is almost exclusively due to its double bond; the chlorine atom, as second functional site, does not react easily. The most important property of VC is its ability to polymerize. It also should be mentioned that peroxidation was repeatedly observed to occur when VC came into contact with atmospheric air due to leakage.[66] Commercially produced VC monomer is in general highly purified; degrees of purity of 99.99 percent are reported. Specific declarations of individual plants state only marginal

amounts of acid (free HCl), acetaldehyde, iron, acetylene, butadiene, water, and stabilizers.[105] Avoiding impurities is a prerequisite since they retard polymerization.[21,105] Liquid VC is stored and transported in steel containers.[5,65,105] Vinyl chloride is used mainly for polymerization, but it is also used as a refrigerating substance, as a propellant for sprays and aerosols, and for a small number of other chemical reactions.[105]

Four *methods of polymerization* are used for industrial fabrication of polyvinyl chloride: emulsion, suspension, bulk, and solvent polymerization.[5,6,21,65,66] Commercially most important were the two older methods of emulsion and suspension polymerization, but now bulk polymerization has been added.[65] In 1972, emulsion polymerization accounted for 78 percent, bulk polymerization for 6 percent, and solution polymerization for 3 percent of the total amount of all PVC resins produced in the United States.[67] Initiation of polymerization is accomplished with compounds that form free radicals at relatively low temperatures,[5] e.g., water-soluble compounds such as peroxide, ammonium, and potassium persulfate for emulsion polymerization or soluble organic compounds, such as lauroyl and benzoyl peroxide, azobisisobutyronitrile and isopropylpercarbonate.[5, 6, 65] Formation of free radicals also occurs by thermal decomposition of peroxide bonding (—O—O—).[65] Physical basis for initiation of free radical chain-polymerization is the homolytic dissociation of a pair of π-electrons (covalent bond) resulting in free radicals that contain single unpaired electrons. The single unpaired π-electron of the free radical obtained from the catalyst then reacts with the π-electrons of the double bond contained in the VC monomer, transforming the VC monomer itself into a free radical and thus propagating the growth of a chain of molecules with a terminal free radical. Chain growth is interrupted by saturation of the terminal free radical, often involving a reaction between two growing chains.[5, 66, 66, 67, 120] The random character of the termination steps accounts for the production of chains of different length and hence different degrees of polymerization with molecular weights statistically distributed around a mean value. One of the operating variables determining specific type of PVC produced is temperature[67] which influences degree and velocity of polymerization as well as vapor pressure. Ordinarily, emulsion polymerization proceeds at temperatures of 40–70°C and total reaction pressure of 8–10 atm.[65]

In *emulsion polymerization* reactors (size: 2000–5000 gallons) are charged with the watery phase, VC is added, the agitator is started, and the emulsion is heated. At termination of the polymerization process the reactor content is emptied into a dump tank. The slurry can then be processed by centrifuging and drying. The dry polymer is separated, screened, and bagged. In *suspension polymerization* water-soluble protecting colloids are added as dispersing agents for stabilization of the suspended vinyl chloride droplets. Subsequent procedures are similar. Unreacted monomer is driven out of the slurry and recovered for recycling.[5,6,65] Suspension PVC is almost pure polymer since additives amount to less than 1 percent and most of that leaves when the slurry is centrifuged. For *compounding*, the powdery or granular polymer is dry-blended under heat and pressure using plasticizers, light and heat stabilizers, and sometimes fillers, lubricants, and pigments or dyes.[5] PVC dry blends are compounded by hot mixing at fusing temperatures. Depending on the type of end product, fusion temperature lies *below* or *within* the softening range (120–160°C). In *calendering* (production of endless sheets) temperatures of 100–120°C for rigid PVC and of 150–180°C for flexible PVC are reached. Tiles are fabricated by *welding* of several layers of calendered sheets in a heated press. In conversion to end products by *extrusion*

(profiles, pipes, conduit, ribbons) temperatures of 150–300°C can be reached. All this shows that temperature ranges, as a rule, from 100–200°C in converting the thermoplastic PVC resin by various procedures.[45,46,132]

Toxicology, Occupational Medicine, Clinical Experience (TABLES 4–6)

Simultaneous with the start of large-scale production of PVC in 1930, pharmacologic properties of vinyl chloride[45,107,127,132] and problems of occupational health[133] were investigated. At first, vinyl chloride appeared to be a suitable narcotic which, even after Oster in 1947[107] and Carr in 1949[45] had observed severe cardiac arrhythmia (believed to be due to potentiation of adrenaline effect[45]), was considered to be one of the least dangerous chlorinated hydrocarbons.[24,30,46,52,132]

With the exception of two communications concerning acute VC intoxication without serious consequence in 2 workers[46,47] no other data on occupational health hazards in PVC production were reported until 1949 when Tribukh *et al.*[140] published results of an investigation at a Russian plastics factory. On examination of a group of 73 workers (48 males, 25 females) engaged mostly in processing PVC polymer (compounding at temperatures up to 160°C and calendering with release of trapped VC, use of chlorinated naphthalenes and diphenylene as plasticizers, effects of PVC dust), the authors found evidence of what they termed a "more or less marked hepatitis," presenting as a slight enlargement of the tender liver but with conspicuous absence of characteristic complaints, jaundice or bilirubinuria. Other findings were: hypotension, anemia, "chronic gastritis," skin lesions, and a peculiar whitish coating of the upper respiratory tract mucosa. This spectrum of symptoms was attributed to the action of plasticizers, and long-term follow-up studies were thought to be necessary, particularly for prevention of later development of serious liver disease. With the exception of liver disease, similar but badly documented findings, also attributed to additives, were reported by Devignevielle,[48] Parmeggiani,[142] and Hervieux and Tessier[49] between 1953 and 1959. Acute intoxication was again reported, this time in Great Britain, with acute collapse during VC polymerization[50] and a second degree burn after direct contact with vinyl chloride.[51] Filatova *et al.*[52,53] were the first to point out a prevalence of "toxic angioneuropathy" in workers engaged in VC polymerization in spite of working area concentrations below Russian maximal allowable concentration (MAC) values (1 mg of VC per liter = 391 ppm). In 1960, Danziger[57] described 3 cases of acute VC intoxication occurring in VC polymerization, 2 of them fatal. Suciu *et al.*[140,141] were the first to give a more detailed analysis of the disease spectrum encountered in 167 workers of two Rumanian PVC-producing plants who had been studied during a 4-year period. Their paper ranks as the earliest description of vinyl chloride disease. Gastrointestinal symptoms dominated; in addition, central nervous system disturbances were found in a number of cases, a Raynaud-like syndrome in 10 workers, contact dermatitis and pseudoscleroderma in another 10, and alteration of thyroid function in 5. The authors found hepatomegaly in 51 and splenomegaly in 10 workers. BSP retention proved to be elevated in 2 of 11 cases examined. Liver biopsy in 2 cases revealed chronic hepatitis. A combination of various symptoms was seen in quite a number of workers. In 1965, Filatova *et al.*[58] again reported on a Raynaud-like syndrome and central nervous system symptoms in PVC workers. Pushin[143] found liver and biliary tract disease in 15 percent of those workers of the Sverdlovsk chemical plant who were engaged in PVC production. On the basis of a clinically slightly enlarged tender liver with mild hyperbilirubinemia occurring in these cases, he diagnosed anicteric, chronic

"epithelial" hepatitis. As possible etiologic factors, primary ingredients for polymerization, compounds released from the polymer during calendering, and plasticizers (phthalates), were discussed. In 1966, Cordier *et al.*[85] were the first to describe acroosteolysis of the distal phalanges combined with a Raynaud-like symptomatology in 2 reactor cleaners (VC polymerization). Subsequently, similar cases were reported in 1967 by Chatelain and Motillon,[86] Marin *et al.*,[87] Bourrichon,[88] Wilson *et al.*,[89] and Harris Adams.[90] With this clustering of publications the disease became known as "occupational acroosteolysis" with typical roentgenologic findings, often combined with Raynaud's syndrome and accompanied rarely by scleroderma-like skin lesions; the disease seemed to occur only in reactor cleaning ("polycleaners' disease").[91-97] Between 1969 and 1972, Anghelescu *et al.*,[7] Filatova and Antonyuzhenko,[98] Dinman *et al.*,[99,100,101] (on the basis of a large-scale epidemiologic study), Lefèvre,[102] Markowitz *et al.*,[103] and Dugois *et al.*[104] observed further cases of this syndrome, occurring only in workers engaged in VC polymerization. It appeared as if processing the polymer would not entail any health hazard (in spite of reflections on the content of trapped substances[91,105-108,110,111,112]). Single deviant observations made in 1970 by McCord[109] and by Misgeld *et al.*[113] in 1973 as well as warnings voiced in the past by Tribukh *et al.*[114] in 1949 and by Danishevskii *et al.*[115] in 1961 obviously were not sufficient to cast doubt on this concept, especially since many standard textbooks had stressed the absolute harmlessness of processing the polymer,[7,105,107,108,110,116,117] apart from the minimal risk attributed to VC inhalation[85, 88, 93, 95, 98, 105, 109] (TABLE 4).

Animal experiments between 1930 and 1963 (TABLE 5) were first limited to the assessment of acute VC toxicity. However, after 1961 four research groups presented results on chronic toxicity of vinyl chloride (TABLE 6) that were not repeated on a large-scale basis. The importance of these results seems to have been underrated, in part even by the authors (e.g., Lester *et al.*[96]) themselves. The experiments of Maltoni *et al.*[97] that up to now were made known only in part, deal essentially with the carcinogenicity of vinyl chloride. These results had been preceded by the experimental work of Viola and co-workers.[122,123] However, results published by Torkelson *et al.*[117] in 1961 induced the German Standards Advisory Committee to reduce MAC standards for vinyl chloride from 500 ppm (in operation since 1966) to 100 ppm in 1970.[94] In 1972, a group of dermatologists at Bonn University were the first in Germany to report on cases of "occupational acroosteolysis" with Raynaud's syndrome and scleroderma-like skin lesions.[75] They found the symptomatology of this disease, however, to be much more complex than was so far assumed and hence proposed calling this syndrome "vinyl chloride disease."[75]

LIVER DISEASE IN PVC WORKERS

Clinical Observations; General Outline

It seems quite remarkable that after the findings of Tribukh *et al.*[114] in 1949 liver damage was only mentioned marginally in subsequently published papers and that no intensive investigation of this feature of vinyl chloride-polyvinyl chloride toxicity had been initiated before 1972. One of the reasons for this late detection of life-threatening liver disease may be the minimal degree of functional hepatic abnormalities generally encountered in these workers which contrasts strikingly with gross morphologic changes seen at peritoneoscopy and with the development of portal hypertension and angiosarcoma of the liver which both are now recognized to be associated with exposure to vinyl chloride.

TABLE 4

CLINICAL MANIFESTATIONS AND FATALITIES AMONG WORKERS IN VINYL CHLORIDE POLYMERIZATION (PM) AND POLYVINYL CHLORIDE PROCESSING (PC) (REVIEW OF LITERATURE)

Author	No. of Workers		Acroosteolysis	Raynaud-like Phenomenon	Skin Lesions	Liver Disturbances	Acute Intoxication (Fatalities)
	PM	PC					
Dublin and Vane (1933, 1941)	2						Slight intoxication
Tribukh *et al.* (1949)	73				—*	21	
Chief Inspector of Factories (1953)	2						Collapse
Harris (1953)	1				1		Second-degree burn
Devignevielle and Fluci.er (1953)	—†				—*	—*(?)	
Parmeggiani and Sassi (1955)	13					—*(?)	
Filatova *et al.* (1957, 1958)	—†			—*			
Hervieux and Tessier (1959)		145			2		
Danziger (1960)	3						1 Slight narcosis, 2 fatalities
Suciu *et al.* (1963, 1967)	168			10	10	51‡	
Filatova *et al.* (1965)	163			—*			
Pushin (1965)	350§					15%¶	
Cordier *et al.* (1966)	123		2	2	2		
		178					
Chatelain and Motillon (1967)	441		5	12			
Marin *et al.* (1967)	528		5	12	5		
Spain	1		1				
Italy	1		1				
Bourrichon	100		5				
Wilson *et al.* (1967)	3,000		31	22	8		
		1,000					
Harris and Adams (1967)	588		2	3	2	1‖	
Anghelescu *et al.* (1969)	300		2	8	5		
McCord (1970)		1	1		1		1 Fatality
Filatova and Antonyuzhenko (1971)	—†		"Chronic occupational poisoning"				
Dinman *et al.* (1971)	3,754		41	23			
		1,257		1			
Kramer and Mutchler (1972)	98					Slight**	
Lefèvre (1972)	780		19				
Markowitz *et al.* (1972)	2		1	2	2		
Dugois *et al.* (1972)	1		1	1	1		
Misgeld *et al.* (1973)		1	1	1	1		

Total	10,056 86 + *x* 12.724	2,582	118	97	40	73	5 Acute intoxications 3 Fatalities

* —, number of abnormal findings not stated.
† —, number of workers not stated.
‡ Liver biopsy in 2 cases—diagnosis "chronic hepatitis;" splenomegaly in 10 cases.
§ 350 workers employed in the Swerdlovsk plastics factory, number of PVC workers contained therein not stated.
¶ Liver disturbances in 6.57 percent (23/350) of 350 chemical plant workers, in 15 percent of PVC workers.
‖ Palpable liver and persistently raised serum bilirubin.
** "Some changes in liver function," with statistically significant correlation of BSP retention and exposure.

TABLE 5
VINYL CHLORIDE EXPOSURE IN LABORATORY ANIMALS—ACUTE TOXICITY (REVIEW OF LITERATURE)

Author	Species*	Concentration (ppm)	Length of Exposure	Effect	Pathology
Patty *et al.* (1930)	g†	200,000–400,000	"Very short time"	Fatal (lethal range)	Lung: edema Liver: hyperemia Kidney: hyperemia
		100,000	30–60 min	"Dangerous to life"	
		5,000	Several h	No severe acute disturbances	
Schaumann (1934)	Starling heart-lung preparation (cat)†	250,000–300,000	?	No cardiac failure	
Schaumann (1938)	m + r†	Slight narcosis	4 h/5–8 d; 1 h/d/4 wk	Narcosis	Liver and kidney: no changes
	d†	100,000	3 h/7 d during 3 wk	Narcosis	Liver and kidney: no considerable changes
Peoples and Leake (1933)	m†	245,000–285,000	10 min	Fatal (lethal range)	
		85,000–125,000	10 min	Minimal anesthetic range	
	d + rb†	170,000	?	Narcosis	"No apparent untoward effects even after prolonged anesthetization"
Oster *et al.* (1947)	d (6)	100,000 (narcosis)	?	Serious cardiac arrhythmias	
Carr *et al.* (1949)	d (7)	? (narcosis)	?	Narcosis: sensitization of myocardium	

Mastromatteo *et al.* (1960)	m (5) r (5) g (5)	100,000	30 min	Deep narcosis—side position with tremors	*Fatal outcome:* Lung: vascular engorgement with hemorrhages and edema
	m (5) r (5) g (5)	200,000	30 min	Deep narcosis (1 mouse dead)	Liver: congestion, partly fatty infiltration (g) Kidney: congestion Clotting defect
	m (5) r (5) g (5)	300,000	30 min	Dead; g in deep narcosis, 1 died hours after exposure	*Survivors:* "Little difference from control animals (liver, kidney, spleen, brain, heart, adrenals, lymph nodes, eyes) except for pulmonary congestion"
	g (5)	400,000	30 min	Deep narcosis, 1 died during, 1 after exposure	
Lester *et al.* (1963)	r†	50,000		Moderate intoxication	
		70,000		Righting reflex lost	
		100,000		Corneal reflex disappeared	"No visible gross pathology"
	r (2)	150,000		Deep narcosis, 1 rat died of respiratory failure	Lung: congestion/edema

* Abbreviations used: r, rats; g, guinea pigs; rb, rabbits; d, dogs; m, mice. Number of animals stated is given in parentheses.
† Number of animals not stated.

TABLE 6
VINYL CHLORIDE EXPOSURE IN LABORATORY ANIMALS—CHRONIC TOXICITY (REVIEW OF LITERATURE)

Author	Species*	Concentration (ppm)	Length of Exposure	Response	Pathology
Torkelson *et al.* (1961)	r (20)	500	7 h/d, 5 d/wk for 4.5 mo	Normal growth	Liver: average weight increase, centrolobular granular degeneration Kidney: interstitial and tubular changes
	r (24) g (9) rb (3) d (1)	200	7 h/d, 138–144 times in 204 d	Normal in appearance, mortality, and growth	Liver: microscopically normal in rats, guinea pigs, and dogs; centrolobular granular degeneration in rabbits (together with necrosis and some foamy vacuolation in male and necrosis with periportal cellular infiltration in female); weight increase of rat livers
	r (5) r (5) r (5) r (5)	200	4 h/d 2 h/d for 6 mo 1 and 0.5 h/d for 6 mo	Normal in appearance, mortality, and growth "Entirely normal"	Liver: average weight increase
	(same procedure as in 200 ppm)	100		Normal in appearance, mortality, and growth	Liver: slight increase of average weight in rats after exposure 7 h/d, 138–144 times in 204 d *and* either 4 or 2 h/d for 6 mo
	r (48) g (24) rb (6) d (2)	50	7 h/d, 130 times in 189 d	Normal in appearance, mortality, and growth	Normal
Lester *et al.* (1963)	r (18)	100,000 80,000	8 h/d for 2 d 8 h/d for 13 d	Narcosis, 10 rats died, initial loss of weight, followed by normal growth ("tolerance to the gas")	Lung: acute focal necrotizing pneumonia, edema, metaplasia Liver: parasitic cysts, moderate to marked swelling of cells, definite fine to medium or large irregular vacuoles, compression of sinusoids Spleen: lymphocytic hyperplasia including most of the interstitium
	r (10)	50,000	8 h/d for 19 d	Initial loss of weight, followed by normal growth ("tolerance to the gas")	Liver: parasitic cysts, marked swelling of cells, large irregular vacuoles or clear spaces, compression of sinusoids, changes focal to diffuse

					Spleen/kidney: no differences between control and experimental animals
	r (30)	20,000	8 h/d, 5 d/wk for 3 mo	Normal in appearance	Liver: parasitic cysts, moderate to marked swelling of cells, definite fine to medium or large irregular vacuoles, compression of sinusoids Spleen: no differences between control and experimental animals Conclusions: 1. The only finding suggesting a specific toxic action of VC is the increase in liver weight on exposure to 50,000 ppm for 19 d and to 20,000 ppm over 92 d 2. Morphological alterations without pathologic significance
Viola (1970)	r (25)	30,000	4 h/d, 5 d/wk for 12 mo	Slightly soporific, normal in appearance and growth After 10 mo loss of weight 13 died from cardiorespiratory complications, 2 from hematoperitoneum	Liver: increased volume, smooth surface, sometimes subicteric, somewhat more brittle consistency than normal Microscopically: *Alteration of hepatocytes* with marked cytoplasmic and nuclear polymorphism (torpid degeneration of the cytoplasm to necrosis) *Proliferation and hypertrophy of Kupffer-cells* *Round cell infiltration of portal tracts* *Blockade of portal capillaries, centrolobular veins and sinusoids* by numerous centrally located areas of partial necrosis *Intensive fibrosclerotic reaction* along areas of degenerative processes *Fatty change* Kidney: signs of tubulonephrosis sometimes accompanied by chronic interstitial nephritis

TABLE 6—*Continued*

Author	Species	Concentration (ppm)	Length of Exposure	Response	Pathology
					Arteries: signs of endothelial fibrosis (with thickening and dissociation of the elastic membrane), often with partial hyaline degeneration and homogenization of the walls and proliferation of endothelium Skin: superficial hyperkeratosis, thickening of epidermis, dissociation of collagen bundles, diminution and fragmentation of elastic reticulum Bones: extensive periosteal proliferation of cartilage-like material (small metatarsal bones) Brain: degenerative lesions of grey and white matter Nerves: surrounded and invaded by fibrotic processes
Viola *et al.* (1971)	r (26)	30,000	4 h/d, 5 d/wk for 12 mo	Slightly soporific, normal in appearance and growth After 10 mo development of paraauricular tumors	Liver: enlarged, very fragile, "severe chronic hepatitis" Kidney: swelling of parenchyma, often tubulonephrosis Lung: interstitial pneumonia Brain: degenerative lesions Tumors: skin in 17 cases; lung in 7; bone in 5
Basalaev *et al.* (1972)	r + rb†	11.7–15.6	?		Cardiovascular disorders Changes in bioelectric activity of hypothalamus Hyperadrenalinemia Osteoporosis and resorption of bone tissue

* Abbreviations used: r, rats; g, guinea pigs; rb, rabbits; d, dogs; m, mice. Number of animals stated is given in parentheses.
† Number of animals not stated.

In December 1972, our colleagues from the Department of Dermatology alerted us to the possible occurrence of serious liver disease in workers of a nearby chemical plant who were engaged in vinyl chloride polymerization and to a smaller degree in processing the polymer to the final plastic product. We started an extensive examination program that included peritoneoscopy and guided liver biopsy because we felt that this procedure might yield deeper insight into nosology and pathomorphology of vinyl chloride-associated hepatic disease than merely blind percutaneous biopsy, since a larger proportion of cirrhotic or fibrotic changes may escape detection if only blind biopsy is employed.[88,139,140]

According to information furnished by the plant physician, a total of roughly 180 workers had in the past been exposed to vinyl chloride in this plant, either as reactor cleaners or in further processing of vinyl chloride (centrifuging, drying, sizing, and bagging the polymer).

To date, we have been able to collect data from a total of 50 workers of this plant (TABLE 7). Their age distribution is shown in FIGURE 1. More than half of them were of non-German origin (nationality: German, 23; Greek, 21; Turkish, 6). Among the 50 workers examined 44 had been working in the polymerization process (39 of them alternatively as reactor cleaners) and 6 in processing the polymer into the final plastic products. The length of exposure (FIGURE 2) ranged from 9 months to 21¾ years for the 44 polymerization workers, with 15 of them having had an exposure of 9 or more years' duration. For the 6 men working in the postpolymerization phase the length of exposure was 13, 9, 5¼, 4½, 4, and 2 years, respectively. Case 50 had been working in the postpolymerization phase for 2 years and subsequently in the manufacture of high-strength paper (hardening by epoxy compounds) at the same plant for 10 years.

Medical History

In the overwhelming majority of cases previous history was uneventful. One worker (case no. 1) had a previous history of jaundice of unknown etiology 18

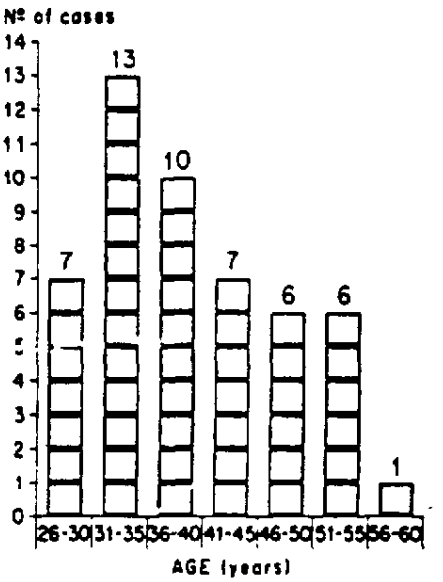

FIGURE 1. Age distribution of 50 PVC production workers (age at examination).

TAB

SYNOPSIS OF ANAMNESTIC, CLINICAL, BIOCHEMICAL, PERIT

Abbreviations used are: *Nationality:* Ger, German; Gr, Greek; Turk, Turkish; *Job Classification:* PM, VC polymerization; PC, processing of the polymer; *Perito-neoscopy:* U, slightly irregular or undulated; G, granular to finely nodular; Nod, coarsely nodular; C, comma-like or stellate; R, finely to coarsely reticular; S, small

No.	Nationality	Age (yr)	Job Classification	Exposure (yr/mo)	Alcohol Intake (g/d)	Central Nervous Symptoms	Upper Abdominal Discomfort	Hepatomegaly*	Splenomegaly*	Serum Bilirubin (>1.0 mg/100 ml)	BSP Retention (>5% after 45 min)	SGOT (>13 (u) mU/ml)†	SGPT (>13(22) mU/ml)†	Alkaline Phosphatase‡
1	Ger	50	PM	21/9	—	+	+	1.5			8.7	15	15 (23)	
2	Ger	56	PM	18/6	16–32	+	+	2	2		6.1			
3	Ger	47	PM	18	—	+		3	5		15.6	13	19 (24)	92
4	Ger	46	PM	17/6	s	+	+			1.1	10.2	13(22)	15 (47)	
5	Ger	51	PM	17	48–64			3	1.5		9.1	19	17	
6	Ger	51	PM	16	16		++	1			11.3			
7	Ger	52	PM	15/3	s	+	+	2	(2)	1.2	16.7	25	22	83
8	Ger	53	PM	14/6	s	+	+	1.5			5.6	15		
9	Ger	44	PM	13/9	s			1.5				15	13	
10	Ger	39	PM	13/9	16		++	3	(11)	2.0	17.6	31	23	85
11	Ger	48	PM	13	16–32		++		1.5		6.2	15	15	
12	Ger	27	PM	12/6	—	+						13		
13	Gr	40	PM	12/3	28		+			1.1			13	
			PC	0/9										
14	Ger	52	PM	11	—	+	+	2	11	1.1	13.0	16	16	
15	Ger	35	PM	9	16				3	1.1	15.1	19	17(31)	50
16	Gr	45	PM	8/6	16						8.8	13	13	
17	Gr	42	PM	6/8	s	+	+	2			13.8	25 (24)	23 (63)	
			PC	4/0										
18	Ger	54	PM	6/6	16	+	+	10	(10)	1.4	6.9	(20)	(27)	>8
19	Ger	31	PM	5/9	16		+						(28)	
20	Turk	33	PM	5/9	s		++					15		
21	Gr	30	PM	5	s		++				9.6	15	13	
22	Ger	34	PM	5	16	+	++		1.5		21.5	21 (21)	23 (40)	
23	Gr	36	PM	5	16		++				7.6		25	
24	Gr	30	PM	5	s	++	++	1.5	6	1.8		90	190	
25	Gr	35	PM	4/9	16	++	++	1.5			8.5	32 (27)	30 (40)	
26	Ger	30	PM	4/9	16–32		++	3			7.5	15	15 (24)	
27	Ger	31	PM	4/9	s	++	++	1.5			8.3	15	15	
28	Gr	31	PM	4/0	—	++	++		6	1.7	7.1	23	25	
			PC	1/0										
29	Turk	33	PM	4/0	s	++	++	6	3	1.8	25.6	25	58	66
30	Gr	30	PM	3/9	4	++	++	1.5			6.4	15	17	
31	Turk	36	PM	3/9	?	+	+	1.5	1.5	2.2	22.5	25	34	68
32	Turk	33	PM	3/6	—			3			6.8	23	17	
33	Ger	32	PM	3/6	4	+	+	6	4		12.5	19	16	
			PC	1/0										
34	Ger	40	PM	3/6	16		+	1.5		1.1	8.6	19 (20)	15 (31)	
35	Gr	31	PM	3/3	8–16		+				5.2	(20)		
36	Gr	38	PM	3/3	8–16 (110–160) §							13	15 (24)	
37	Gr	47	PM	3/0	16	++	++	3			9.7			
38	Gr	30	PM	3/0	—	++	++	3				13		
39	Turk	30	PM	2/9	—			1.5			8.4	17	13	
40	Gr	33	PM	2/6	—			1	1					
41	Gr	41	PM	2/3	16	+	++	1						
42	Ger	41	PM	1/9	s						6.1	19 (22)	17 (47)	
43	Gr	36	PM	1/6	s			3			6.3	17	17	56
44	Turk	33	PM	0/9	s						5.1	28	30 (23)	66
			PC	0/3										
45	Gr	48	PC	13/0	14		+	7			9.1	13 (33)	13 (80)	
46	Gr	44	PC	9/0	28						15.1	15	17	
47	Gr	39	PC	5/3	16		+					(20)		58
48	Gr	45	PC	4/6	—		+				8.8	(22)	(47)	
49	Gr	37	PC	4/0	44	+		6			7.0	(88)	(72)	110
50	Ger	36	PC	2/0	32	+	+	8				28 (20)	28 (38)	

* Centimeters below costal margin.
† For explanation see TABLE 11.
‡ For explanation see text.

Le 7

...NOSCOPIC, AND HISTOLOGIC DATA OF 50 PVC WORKERS

...ear-like patches to broader concave postnecrotic scars; PC, patchy "perihepatitis ...artilaginea;" A, augmented; B, increased; *Histology:* (+), minimal; +, slight; ++, moderate; +++, marked.

Acrosteolysis	Raynaud-Like Phenomenon	Skin Lesions	Peritoneoscopy: Surface relief	Peritoneoscopy: Capsular fibrosis	Peritoneoscopy: Capsular vessels	Histology: Collagenization of sinusoidal walls	Histology: Enlargement and/or proliferation of hepatic cells	Histology: Septal fibrosis	Spleen Size by Scintigraphy (cm)	Enlargement of Spleen	Esophageal Varices	Thrombocytopenia (<150 X 10³/mm³)
				R		(+)	+		Normal (liver scan)			+
	(+)		G/Nod	R	?/I	+	+	+	15 x 11 x 12	+		+
				R	?	+	++	+	Markedly enlarged (liver scan)	+	+	+
			U/G	R/S	A	+	+		12 x 7 x 11	+		
			Nod	R/S	A	+	+		14 x 12 x 6	+	+	+
	+		G	R/S		+	+	(+)	12 x 9 x 9	+		
	(+)		U	?	?	+	(+)	+	Splenectomy (15 x 12 x 7)	+	+	+
			G	R/S		(+)	++	+	10 x 8 x 4			+
			U	R		+	(+)	+	10 x 8 x 5			+
			G	R/S	I	(+)	+		24 x 12 x 7	+	+	+
			G/Nod	R/S	I	+	+		15 x 11 x 7	+		+
			G	R/S	A	+	(+)	(+)	14 x 5 x 12	+		+
				R		(+)	(+)		Normal (liver scan)			+
		+	G	R	I	+	+++	+	23 x 14 x 9	+	+	+
			G		A	Not examined			13 x 10 x 5	+	+	+
				S		+	(+)	(+)	12 x 9 x 5	+		+
			U	R	A	+	(+)		Normal (liver scan)			
			G	?	?	+	(+)	++	Splenectomy (500 g)	+	+	+
			G	S	A		(+)	(+)	23 x 10 x 18	+	+	+
			G	C/R		+	(+)		18 x 11 x 12	+		+
						+	(+)		14 x 12 x 13	+		+
+		+	Not examined			(+)	+		15 x 9 x 10	+		+
				R		+	+		14 x 9 x 10	+		+
				R		+	(+)		17 x 12 x 14	+	+	+
				R		+	(+)	+	13 x 10 x 10	+		+
			U		A	+	+	(+)	14 x 6 x 8	+		+
				R		+	+		13 x 9 x 14	+		+
			U	S/PC	A		(+)		16 x 10 x 4	+		+
+	(+)	+	G	R					14 x 13 x 6	+		+
				R	A	(+)	+	(+)	Normal (liver scan)			+
+	+	+	G	?	A	+	+		14 x 6 x 11	+		+
+	(+)	+		R	A	+	(+)		13 x 5 x 11	+		+
+	(+)	+	U/G	S		+	+		14 x 9 x 7	+	+	+
	+	+		R	I	+	+		Slightly enlarged (liver scan)	+		+
				C	A	+	(+)		13 x 7 x 9	+		+
			U	C		+	(+)		10 x 9 x 7	+		+
				(S)	A		(+)		12 x 6 x 8	+		+
				C/R		+	+		15 x 12 x ?	+		+
							+		16 x 6 x 8	+		+
			U	C/S	A	+	(+)		13 x 7 x 12	+		+
			G/Nod	C/R/PC	A		(+)		11 x 7 x 10.5	+		+
			O/Nod	S		+	+	+	12 x 9 x 7	+		
				R			(+)		11 x 8 x 5			+
							+		12 x 8 x 6	+		+
							(+)		Normal (liver scan)			
				(R)			(+)		9 x 6 x 6			+
				(R)		(+)	(+)		12 x 8 x 9	+		
				R/PC	A	+	(+)		Normal (liver scan)			+
				S	A	+	+		11 x 5 x 7			
				C	A	+	(+)		12 x 6 x 11	+		

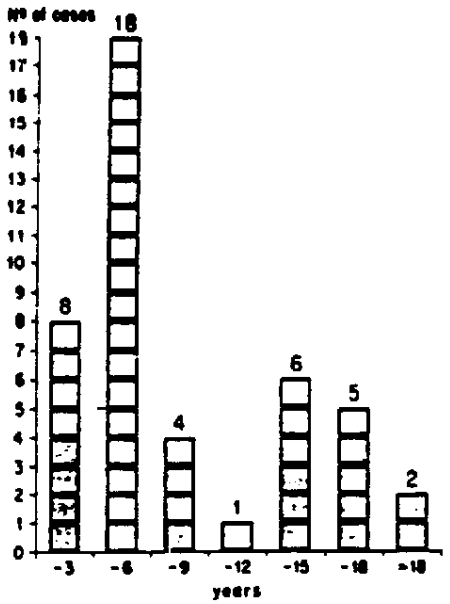

FIGURE 2. Length of exposure in 44 workers engaged in the polymerization process.

years prior to examination (length of exposure: 21¾ years), and "chronic liver disease" was diagnosed in 1968. In 3 cases a symptomless solitary biliary calculus was found on cholecystography (case nos. 43, 45, 50). In one Greek laborer (case no. 48), who had been engaged in the postpolymerization phase of production for 4½ years and who in the past 2 years had repeatedly been hospitalized for gastric ulcer, the present examination by barium meal and gastroscopy revealed a small anaplastic carcinoma of the stomach for which he underwent subtotal gastric resection. A German worker (case no. 18) had partial gastrectomy in 1971, shortly before splenectomy was performed, because of an acute episode of bleeding from an endoscopically diagnosed pyloric ulcer; he also had esophageal varices. One Greek worker (case no. 38) suffered from a mild form of hemophilia A, discovered at appendectomy in 1971; he had no episodes of spontaneous hemorrhage and factor VIII levels ranged between 18 and 50 percent. Another Greek worker (case no. 49) was admitted to the ENT-Department primarily because of deafness of sudden onset, combined with labyrinthine disease; because of elevated transaminase levels he was later referred to the Medical Department.

None of the workers had a history of alcoholism. Ten did not use alcohol in any form (TABLE 8). Alcohol intake was not stated in one case. One Greek worker (case no. 36) had formerly consumed 110–160 g/day as wine but since entering the plant had reduced his intake to 8–16 g. Several laborers had noticed an aversion to alcoholic beverages or an alcohol intolerance after entering the plant.

Complaints

No clear-cut abdominal symptomatology was found. Complaints were usually not suggestive. Fifteen workers reported only slight upper abdominal discomfort.

TABLE 8
ALCOHOL CONSUMPTION IN 50 PVC WORKERS

Reported Alcohol Intake (in g ethanol/d)	No.
None	10
Up to 8 g	15
Up to 16 g	16
Up to 32 g	6
Up to 64 g	2
Not stated	1
Total	50

TABLE 9
GASTROINTESTINAL BLEEDING (ESOPHAGEAL VARICES) AND SURGICAL INTERVENTION IN 50 PVC WORKERS

	No.
Gastrointestinal bleeding	4/50
Splenectomy	3/50
Splenorenal shunt	1/50
Gastric resection for anaplastic carcinoma	1/50

Another 24 claimed to have experienced temporary central nervous symptoms, such as dizziness, slight disorientation, disturbance of vision, and mild headache, often combined with nausea and mild upper abdominal discomfort. Twelve workers spontaneously reported to have smelled "the gas" occasionally which they claimed had a faintly sweet odor. A Raynaud-like symptomatology was reported in 8 cases. Four had experienced episodes of bleeding from esophageal varices during the past 2 years (TABLE 9).

Methods of Investigation

Besides physical examination, a broad spectrum of laboratory tests was applied to each case (TABLE 10). X-ray examination of the upper gastrointestinal tract and intravenous cholecystography were carried out in all cases as were a plain chest film and an ECG with 12 leads. In 3 cases esophagogastroscopy was done. Scintigraphy of liver and spleen was performed in 48 cases.

Peritoneoscopy and guided liver biopsy were performed by us in 41 workers, peritoneoscopy without biopsy in one, and percutaneous blind needle biopsy in two other cases (total: 44 cases). Data of case 14 were put at our disposal by courtesy of Dr. Harald Heuning* who, during a 3-year follow-up including three peritoneoscopies, had previously classified the case as noncirrhotic portal fibrosis with portal hypertension of unknown etiology. We were given access to data of cases 10, 24, 29, and 31 which had been examined by peritoneoscopy and biopsy at the Medizinische Universitäts-Poliklinik†; 1 of these 4 cases (case no. 10) later

* Head, Klinik Föhrenkamp of the Federal Board for Employee's Insurance, D-241 Mölln, Germany.

† We would like to thank Prof. Dr. F. Krück, Direktor der Medizinischen Universitäts-Poliklinik, Bonn, and Prof. Dr. A. Gütgemann, Direktor der Chirurgischen Universitätsklinik, Bonn, for permission to include data of 3 and 2 cases, respectively.

TABLE 10
SPECTRUM OF LABORATORY TESTS PERFORMED IN 50 PVC WORKERS

1. Blood sedimentation rate; hemoglobin; red cell count; white cell count; differential cell count; hematocrit reading; number of platelets
2. Total bilirubin
3. Glutamic oxaloacetic transaminase
4. Glutamic pyruvic transaminase
5. Alkaline phosphatase
6. Lactic dehydrogenase
7. Cholinesterase
8. Thymol turbidity
9. Total protein
10. Serum electrophoresis
11. Bromsulfalein retention

12. Urinalysis
13. Blood urea nitrogen
14. Serum creatinine } only in some cases
15. Serum uric acid }

16. Serum iron
17. Serum copper
18. Blood glucose
19. Total cholesterol
20. Serum triglycerides
21. β-Lipoproteins

22. Blood coagulation factors (II, V, VII, X, antithrombin, thrombin time, thrombelastogram)
23. Hepatitis-associated antigen and antibody

underwent splenectomy after repeated hemorrhage from esophageal varices. In a last case (case no. 7) splenectomy and lienorenal anastomosis were done at the Chirurgische Universitätsklinik.† Histology of the spleen was available in 3 cases after splenectomy; in another 8 cases we performed guided biopsy of the spleen for light microscopy; in 5 of these cases material for electron microscopy was also obtained. In addition, liver biopsy material was obtained for electron microscopy from 8 patients.

Results

Physical Examination

On palpation, the liver was found to be slightly to markedly enlarged in 31 cases. Palpable splenomegaly was noted in 16 cases, in 4 of which it was not accompanied by hepatomegaly. Jaundice, spider angiomata, palmar or plantar erythema or physical demonstrable ascites were not found.

Laboratory Tests

The most consistently positive biochemical test was 45-min BSP retention (TABLE 11). A marginally to markedly pathologic retention was seen in 38 patients with a mean value of 10.5 percent. In 12 cases serum bilirubin levels were marginally elevated (maximum: 2.2 mg/100 ml). Likewise, activities of serum alkaline phosphatase were increased slightly in only one-fifth of the total. Activities of serum aminotransferases GOT and GPT were unequivocally pathologic

TABLE 11
RESULTS OF LIVER TESTS IN 50 PVC WORKERS (CLASSIFICATION BASED ON MAXIMAL VALUES OBTAINED IN MULTIPLE DETERMINATIONS)

	45-Min BSP Retention (5.0%)*	Serum Bilirubin (1.0 mg/100 ml)*	Alkaline Phosphatase† (40 mU/ml)*
Normal	12	38	40
Pathologic	38	12	10
(Range)	(5.1–25.6%)	(1.1–2.2 mg/100 ml)	(50–110 mU/ml)
(Mean)	(10.47%)	(1.4 mg/100 ml)	(71.9 mU/ml)

	GOT‡	No. of Cases		GPT‡	No. of Cases	
Definitely normal	−12 mU/ml§ −19 mU/ml¶	4		−12 mU/ml§ −22 mU/ml¶	11	
Marginally normal	12–20 mU/ml 20–30 mU/ml	31		12–20 mU/ml 23–30 mU/ml	22	
Pathologic	20–50 mU/ml	13	15	20–50 mU/ml 31–60 mU/ml	12	17
	31–60 mU/ml					
	>50 mU/ml >60 mU/ml	2		>50 mU/ml >60 mU/ml	5	
Total		50			50	

* Upper limit.
† Modification of the method described by O. A. H. Bessey *et al.* J. Biol. Chem. 164: 321, 1946; upper normal limit (adults): S. J. Walter and R. Glöckner. Ärztl. Lab. 10: 220, 1964.
‡ Owing to a change in methods of determination of enzyme activities during the investigation (later use of a substrate-optimated method) two sets of reference values had to be used.
§ E. and F. W. Schmidt. Enzymol. Biol. Clin. 3: 1, 1963.
¶ Substrate-optimated standard method, W. Thefeld *et al.* Deut. Med. Wochschr. 99: 343, 1974.

in 15 and 17 cases, respectively; however, marginal values may occasionally be the only and earliest biochemical indication of toxic liver damage.[100]

A more or less marked thrombocytopenia (less than 150,000 platelets/mm³) was observed in 42 cases. Except for 1 patient with splenomegaly (case no. 4) who had leukopenia besides thrombocytopenia, hematologic results were otherwise within normal limits. Tests for hepatitis-associated antigen and antibody were negative in all cases. All other biochemical tests including initially introduced but later abandoned immunologic reactions failed to contribute to the problem in question.

Roentgenology; Endoscopy of Upper Gastrointestinal Tract; Scintigraphy

A diagnosis of esophageal varices, in some cases combined with varices located in the cardiac region of the stomach, could be made in 10 workers; in 5 of them this was done by barium meal, in 2 by x-ray plus endoscopic examination, in 1 by barium meal and splenoportogram, in 1 by endoscopy and splenoportogram, and in the last patient by indirect splenoportography. Only in one case (case no. 7) was intraoperative measurement of portal pressure possible, and

TABLE 12
SPLENOMEGALY IN 50 PVC WORKERS
Spleen size as measured by scintigraphy in 48 cases

Methods:
Splenic scanning by ^{197}Hg-BMHP (40 cases) (normal diameters: 11 x 7 x 4 cm)
Liver scan by ^{99m}Tc sulfur colloid (46 cases)

A. Within normal limits (4 of the cases = PVC-processing workers): 11/48*
B. Exceeding normal limits (2 of the cases = PVC-processing workers): 37/48†
C. Not examined (previous splenectomy): 2/50

Splenectomy in 3 cases

Diameters, weight:
1. 15 x 12 x 7 cm (300 g)
2. Ruptured at splenoportography (500 g)
3. 23 x 13 x 6 cm (1250 g) (scintiscan = 24 x 12 x 7)

* In 6 of the 11 cases by liver scan.
† In 2 of the 37 cases by liver scan.

this proved to be only slightly elevated. Otherwise, no determinations of intrasplenic pressure or of wedged hepatic venous pressure have been carried out so far.

In 5 cases a diagnosis of acroosteolysis was established by x-ray examination of hands and feet.

Approximate spleen size was determined by means of selective scintigraphy using labeled mercury (^{197}Hg-labeled bromomercury hydroxy propane)‡ in 40 cases. Measurement of three diameters (length, breadth, depth) allowed detection of even minor degrees of splenomegaly.[34,47,48,128] The organ proved to be slightly to markedly enlarged in 37 out of 48 cases (total assessment of spleen size: 39 out of 50), a proportion that was considerably larger than that obtained by either physical or peritoneoscopic examination (TABLE 12).

Peritoneoscopy and Liver Biopsy

In internal medicine, the paramount advantage of peritoneoscopy lies in the fact that it permits direct inspection of the abdominal cavity and of size, coloring, surface structures, and circumscribed lesions, especially of the two main hepatic lobes and the spleen which, otherwise, can only be accomplished by exploratory laparotomy. Besides inspection of abdominal organs, the method also allows, although only to a limited extent, minor intraabdominal manipulations such as guided biopsy of liver and spleen, determination of organ consistency by probe, and removal of strand-like adhesions. If contraindications are strictly adhered to, serious complications are rare.[37,129] Based upon a compilation of 63,845 cases in which peritoneoscopy was performed with 48,766 guided liver biopsies, Brühl[37] calculated a mortality rate of 0.029 percent. The rate of complications was 2.49 percent, two-thirds of which, however, had been only of minor importance.

In the cases presented here, *peritoneoscopic findings* were categorized according to the following criteria:

1. *Symptoms of hepatic enlargement.* These were measured by the relation of

‡ We wish to thank Prof. Dr. C. Winkler, Direktor des Instituts für Klinische und Experimentelle Nuklearmedizin an der Universität Bonn, for permission to use results of scintigraphic examinations carried out at his institute.

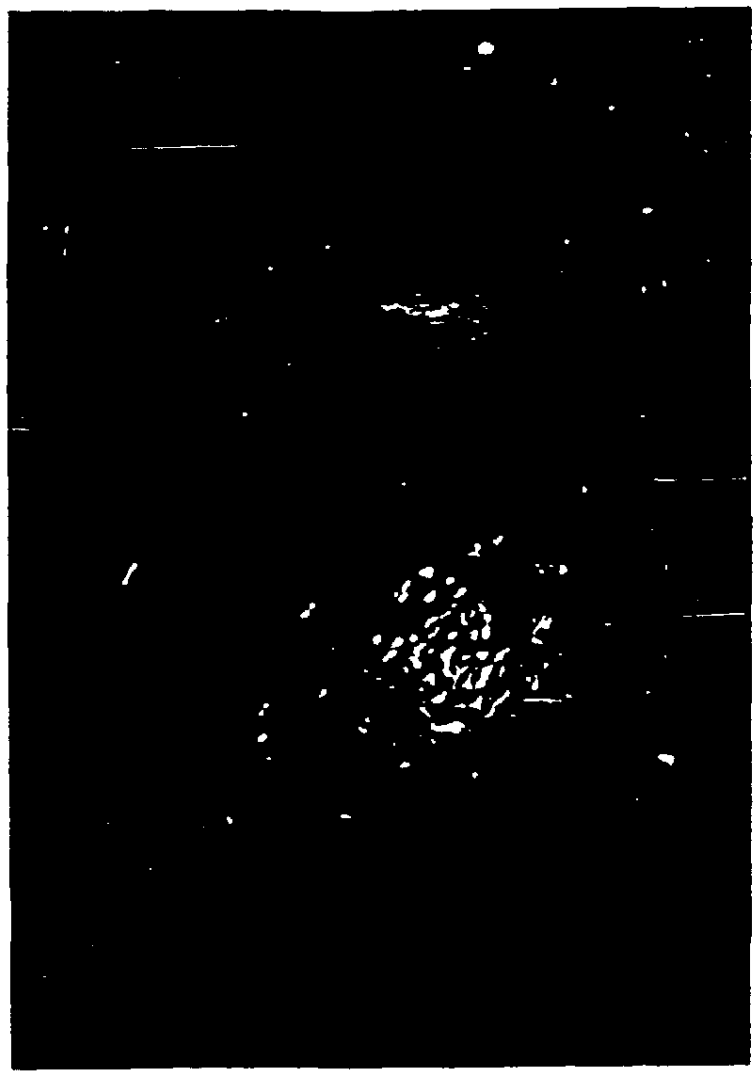

FIGURE 3. Granular appearance of liver surface (conspicuous scattering of light reflection), pronounced coarsely reticular fibrosis of Glisson's capsule, patchy cicatricial fibrosis, distinctly increased capsular vessels. At left upper corner site of guided liver biopsy can be seen. (Case no. 41; length of exposure, 2¼ years.)

lower edge of right hepatic lobe to costal margin and a rounding-off of the normally sharp edge.

2. *Changes in hepatic surface relief.* Hepatic surface relief is normally smooth and glossy with well-defined lobular configuration, mirror-like capsule, and sharply defined light reflection; slightly uneven (irregular) or undulated appearance due to shallow concavities in connection with slight initial cicatrization; granular (FIGURE 3) appearance as initial stage of distortion of hepatic lobular architecture, characterized and recognizable by scattering of light

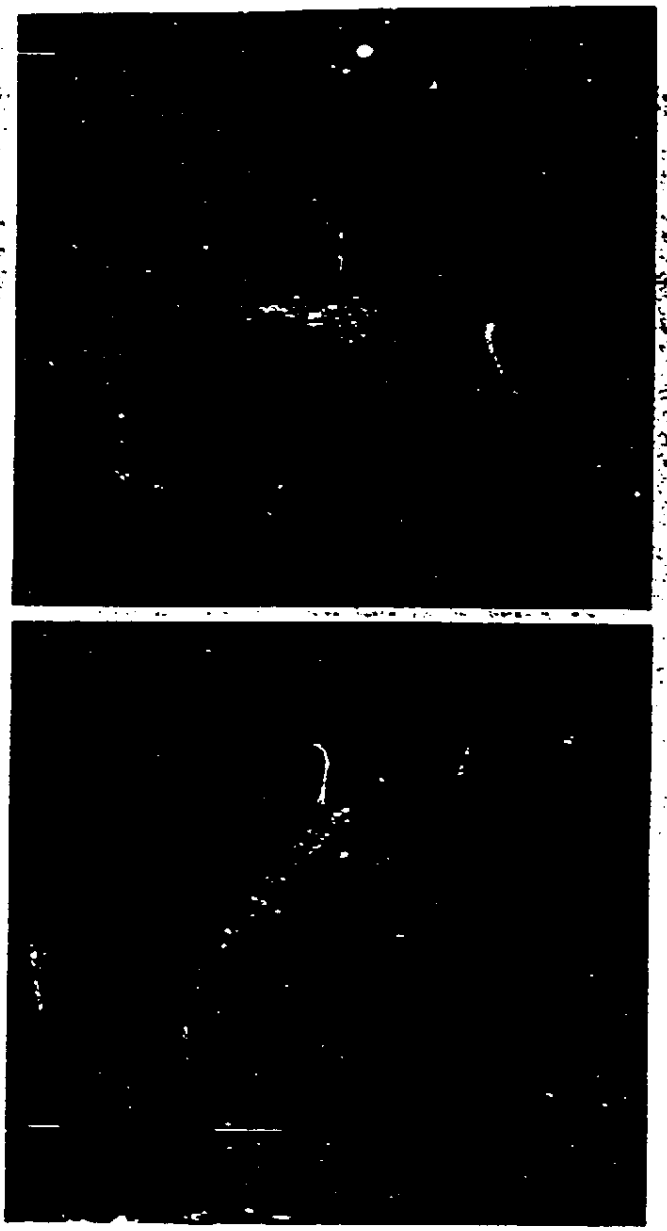

FIGURE 4. a. Finely nodular surface of the liver. Close-up view of lower edge of left lobe. (Case no. 4; length of exposure, 17½ years.) b. Finely nodular appearance of underside of right hepatic lobe with stellate capsular fibrosis and small scars in a worker engaged in processing the polymer. (Case no. 48; duration of job assignment, 4½ years.)

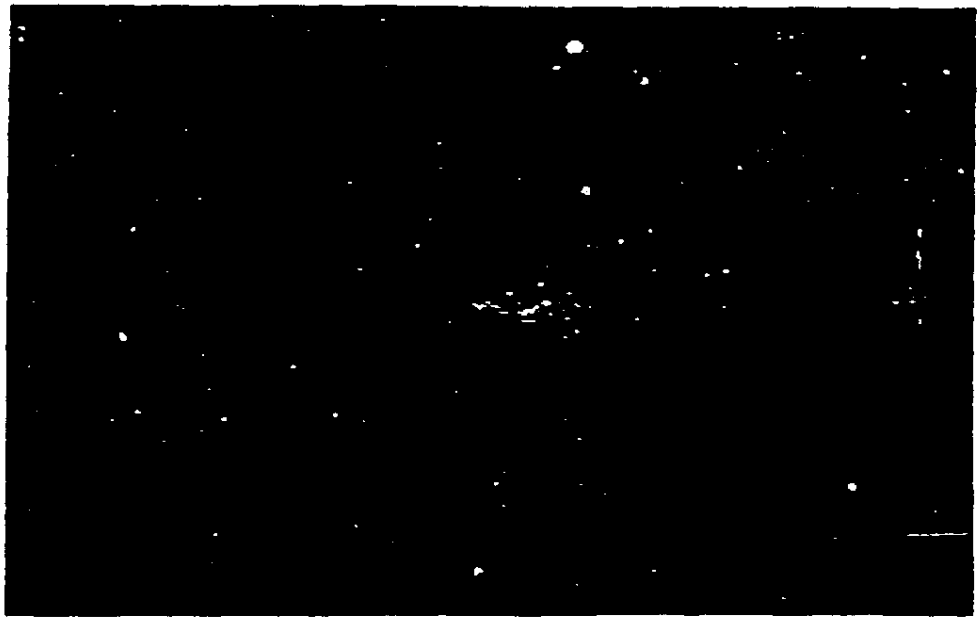

FIGURE 5. Coarsely nodular hepatic surface resembling advanced cirrhosis; left lobe. Histologically there was, however, only septal fibrosis and collagenization of sinusoidal walls. No evidence of portal hypertension. (Case no. 42; length of exposure, 1¾ years.)

reflection, proceeding through finely nodular (FIGURE 4) to eventually coarsely nodular surface relief (FIGURE 5).

3. *Presence of different degrees of local or diffuse hepatic capsular fibrosis.* The capsule is a very subtle indicator of pathologic processes taking place in the underlying tissue.[20] Capsular fibrosis (FIGURE 6) was usually irregularly distributed but mostly less pronounced toward the convexity; in its mildest form it was characterized by a strand-like or membranous opacity. In some cases we noticed a peculiar comma-like or stellate fibrosis (FIGURE 7), probably corresponding to a delicate scarring process in the underlying hepatic tissue. A more pronounced lesion seemed to be the development of a thinly or coarsely outlined more or less elevated network of thickened capsular connective tissue covering the surface (FIGURE 8). In other cases there were several or numerous small scar-like lenticular patches (FIGURE 9) or broader slightly concave cicatricial lesions probably indicating postnecrotic scarring. In 4 cases focal whitish capsular thickening resembled what is known as focal "perihepatitis cartilaginea" (FIGURE 10).
4. *Appearance of capsular vessels.* Capsular vessels are normally not visible; pathologically, they may be slightly augmented or conspicuously increased (FIGURE 11) as an indication of underlying inflammatory processes of various activity.
5. *Symptoms of splenic enlargement and perisplenitis.* Visualization of the spleen by peritoneoscopy is not always possible, even after extreme tilting of the table because the organ may be covered by adipose greater omentum; in this case an effort to bare the lower pole by inserting a palpation probe is some-

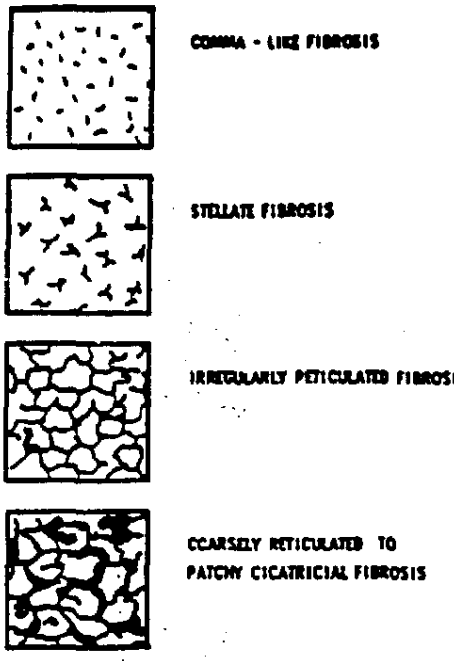

FIGURE 6. Types of capsular fibrosis of the liver observed in PVC workers.

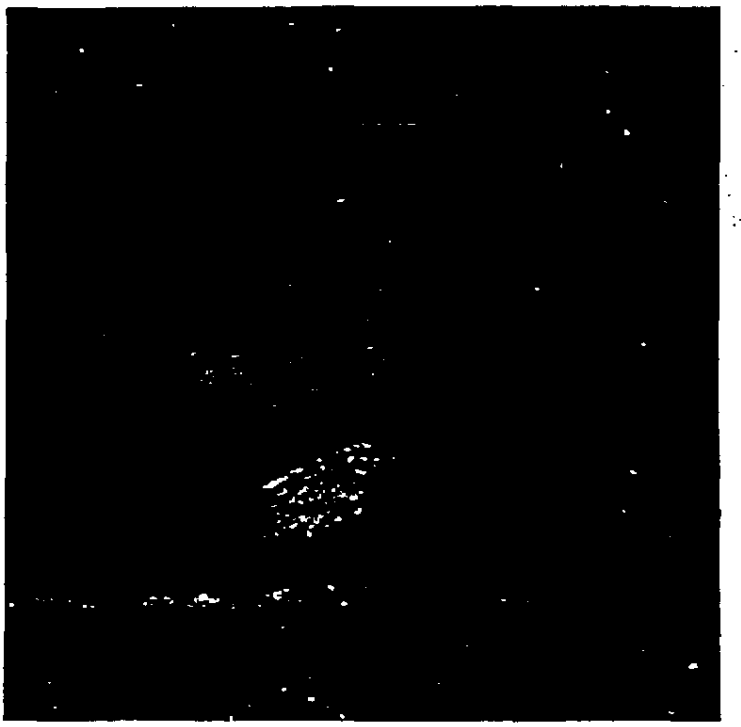

FIGURE 7. Typical comma-like capsular fibrosis on convexity of left hepatic lobe near falciform ligament (top center); in contrast to finely nodular lower anterior edge (see FIGURE 4a) of left lobe, surface on convexity is comparatively smooth. (Case no. 4; length of exposure 17½ years.)

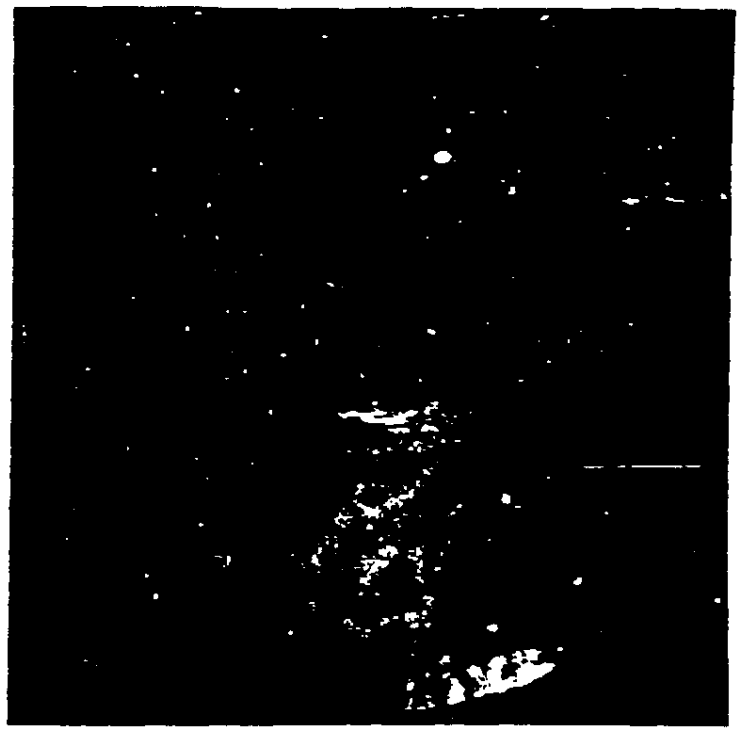

FIGURE 8. Coarsely reticular fibrosis of Glisson's capsule; right lobe. (Case no. 9; length of exposure, 13¾ years.)

FIGURE 9. Lentil-shaped and patchy irregular milk-white capsular thickening near lower edge of right hepatic lobe. (Case no. 16; length of exposure, 8½ years.)

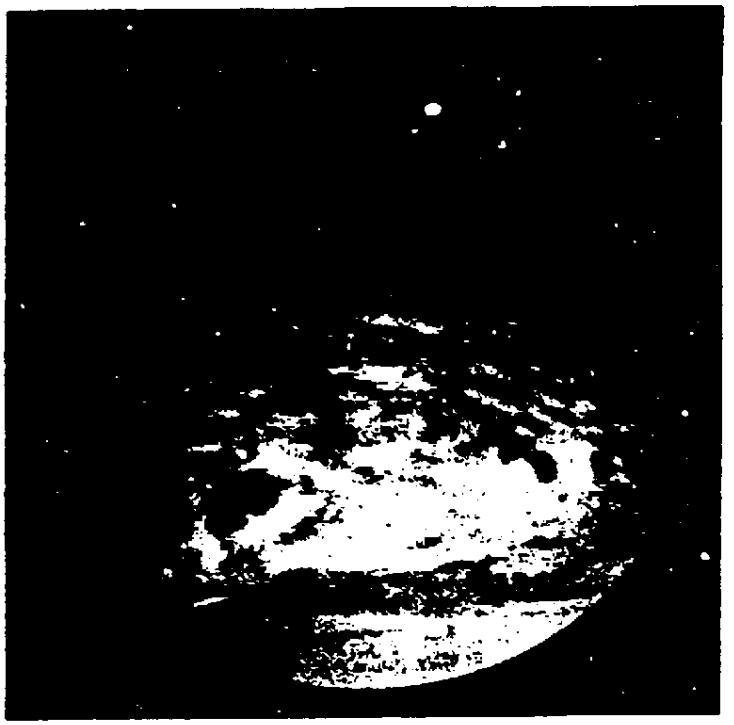

FIGURE 10. Coarsely reticulated fibrosis and patchy focal whitish capsular thickening (focal "perihepatitis cartilaginea"), resembling capsular alterations seen in thorotrastosis of the liver.[16] (Case no. 6; length of exposure, 16 years.)

FIGURE 11. Particularly pronounced increase of capsular vessels in case no. 14 (length of exposure, 11 years) with finely to coarsely nodular surface. The case was formerly diagnosed as "noncirrhotic portal fibrosis and portal hypertension of unknown etiology." Close-up view shot with a special magnifying peritoneoscope (Courtesy of Dr. Henning; see text.)

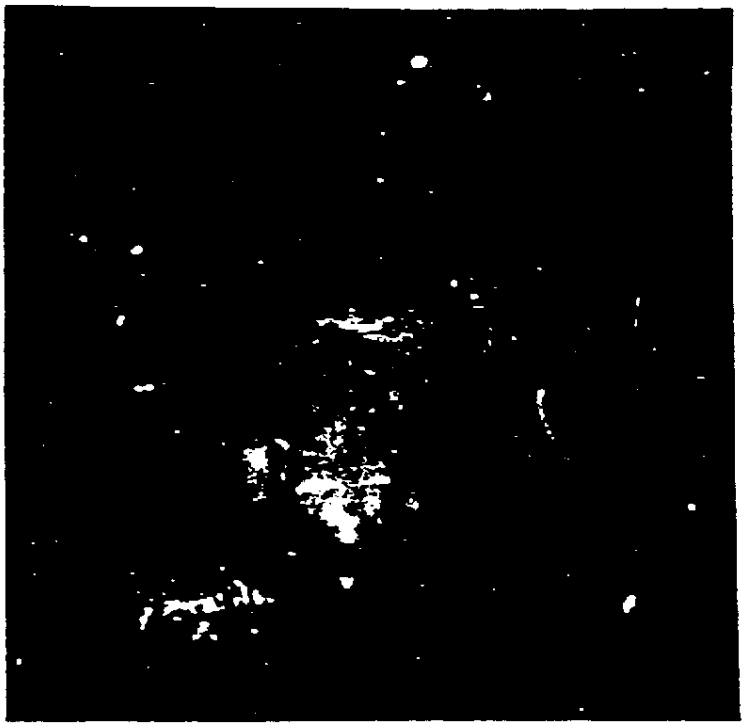

FIGURE 12. Crenate margin of enlarged spleen; lentil-shaped thick milk-white perisplenitic fibrosis and millet-sized subcapsular hemorrhages. (Case no. 5; length of exposure, 17 years.)

times successful. For assessing the spleen size, the relation of the inferior pole of the spleen to the left costal margin and to the phrenocolic ligament as well as the inspection of the crenate margin are useful. Minor degrees of splenic enlargement cannot be recognized by peritoneoscopy. In marked splenomegaly the crenate margin is deeply indented. The splenic capsule seems to be equally sensitive to processes going on in the underlying tissue as is Glisson's capsule of the liver. In a number of cases minor degrees of perisplenitis were present in the form of pinhead-sized to somewhat larger lentil-sized sharply delineated white capsular plaques (FIGURE 12); only rarely were there patches of thick white coating resembling focal "perisplenitis cartilaginea." It is noteworthy that patchy perisplenitis was found only in connection with more or less marked splenomegaly.

6. *Symptoms of portal hypertension.* Quite early in the development of a collateral circulation due to portal hypertension a marked dilatation and later a tortuosity of preformed peritoneal venous vessels can be detected in the falciform ligament, on the anterior stomach wall, on the small and large intestine, and especially accompanying intra-abdominal adhesions. Minimal amounts of ascites can be observed to accumulate between the right hepatic lobe and the abdominal wall if the table is tilted accordingly.

All the lesions described above are nonspecific alterations not suggestive of a distinct etiology.

Changes in hepatic surface relief, degree of capsular fibrosis, and appearance

TABLE 13
HEPATIC SURFACE ALTERATIONS OBSERVED ON PERITONEOSCOPY ($n = 47$) OR AT LAPAROTOMY ($n = 2$)

Alterations	No.	
Surface relief		
A. Smooth	24/49	
B. Slightly irregular or undulated	7/49	
C. Granular to finely nodular	13/49	25/49
D. Coarsely nodular	5/49	
Capsular fibrosis (irregularly distributed)		
A. None	6/46	
Predominantly:		
B. Comma-like or stellate	3/46	
C. Finely to coarsely reticular	20/46	
D. Small scar-like patches to broader concave post-necrotic scars	14/46	40/46
E. Patchy "perihepatitis cartilaginea"	3/46	
Capsular vessels		
A. None (normal)	23/46	
B. Slightly augmented	18/46	23/46
C. Conspicuously increased	5/46	

of capsular vessels on the liver surface were recorded and graded on a severity scale. TABLE 13 shows that in about half of the cases the surface relief of the liver was altered ranging in degree from slightly uneven to coarsely nodular, the macroscopic appearance of the liver being suggestive of advanced cirrhosis in 2 cases (see FIGURE 5). Similarly, capsular vessels were considered to be slightly to conspicuously increased in half of the total cases. The most consistently positive feature of gross pathology was capsular fibrosis. It was unevenly distributed, sometimes more pronounced on the left lobe than on the right one, and in the majority of positive cases it was present in the form of a more or less conspicuous reticulated capsular thickening.

In cases with massive patchy perihepatitis the picture was reminiscent of hepatic "thorotrastosis" (see FIGURE 10).[36] The proportion of peritoneoscopically determined enlargement of liver and spleen can be seen from TABLE 14. Pronounced symptoms of portal hypertension were observed in 7 cases. A small amount of ascites was found in only 1 case.

In contrast to gross morphology, however, *histologic lesions* observed in liver biopsy material were far less pronounced than might have been expected from peritoneoscopic appearance, and this also applies to the cases which laparoscopically resembled advanced cirrhosis of the liver.

In essence, four histopathologic features could be observed (TABLE 15):

a. Degenerative alterations of hepatocytes, occasionally accompanied by phenomena of cytoplasmic adaptation.
b. Slight fibrosis and collagenization of sinusoidal walls.
c. Polymorphism and polyploidy of liver cell nuclei.
d. Activation and proliferation of littoral cells lining sinusoids.

Degenerative alterations of liver cells, manifest within relatively sharply defined intralobular areas (FIGURE 13), were predominantly characterized by hydropic swelling and granularity of cytoplasm, with occasional single cell necrosis, and were present, to some degree, in all the cases examined. In some cases *adaptive changes* manifested themselves as "ground glass appearance" of cyto-

TABLE 14

HEPATOSPLENOMEGALY AND SYMPTOMS OF PORTAL HYPERTENSION ON PERITONEOSCOPY OR AT LAPAROTOMY

Hepatomegaly (n = 49)		Splenomegaly (n = 36)		Symptoms of Portal Hypertension (n = 49)	
None	31/49	None	13/36	None	40/49
Present	18/49	Present	23/36	Questionable	2/49
		Spleen not visualized*	13/49	Marked	7/49

* In 13 cases the spleen could not be visualized during peritoneoscopy even after extreme tilting owing to its being covered by nonremovable omental fat.

TABLE 15

SYNOPSIS OF PERTINENT HISTOLOGIC FEATURES IN 49 PATIENTS

	Collagenization of Sinusoidal Walls	Enlargement and/or Proliferation of Littoral Cells	Septal Fibrosis	Fatty Change
None	10	1	34	26
Present in	39	48	15	23
Grading				
Minimal	7	25	6	6
Slight	32	20	8	14
Moderate	—	2	1	3
Marked	—	1	—	—

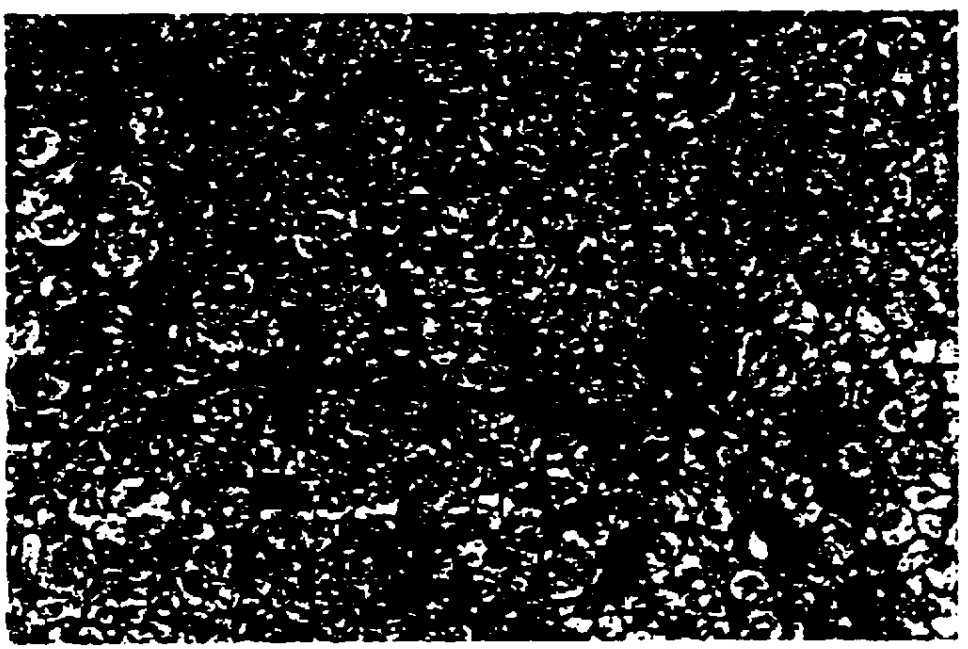

FIGURE 13. Degenerative changes of hepatocytes with hydropic swelling and granularity of cytoplasm. Occasional single cell necrosis. Note proliferation and pleomorphism of littoral cells (Case no. 14; length of exposure, 11 years; biopsy several days after last exposure). H&E (×235).

FIGURE 14. Micronodular appearance due to septal fibrosis with characteristic hydropic swelling of parenchymal cells (Case no. 5; length of exposure, 17 years; biopsy 2 weeks after last exposure). Trichrome Goldner stain (×94).

plasm. *Fibrosis*, observed in somewhat less than one-third of the cases, was partly septal, partly portal, and partly midzonal; in 80 percent of the cases there was collagenization of sinusoidal walls, occasionally forming a network-like intralobular fibrosis (FIGURE 14). *Polymorphism of liver cell nuclei* was characterized by enlargement and polyploidy of nuclei. The total number of bi- or multinucleated cells, however, did not seem to be increased. A rather characteristic feature was an *activation and proliferation of sinusoidal cells*. There was a definite increase in the number of littoral cells; they were occasionally arranged in a chain-like fashion and often resembled short pegs. In 6 patients, a bizarre nuclear shape was observed with enlargement and hyperchromatism (polyploidy?), interpreted as a symptom of pronounced cytologic deviation (FIGURE 15). Less than half of the cases had predominantly minimal to slight fatty infiltration of hepatocytes, not correlated to either length of exposure or drinking habits. More detailed information on special features of histology may be found in Dr. Gedigk's paper.

DISCUSSION

Our synopsis of prior studies published between 1933 and 1973 (TABLE 4) includes a total number of about 12,500 workers employed in VC polymerization and PVC processing. However, considering the relatively high standards of occupational hygiene in modern chemical industry,[12,20,29,70,144] the true number of workers examined routinely by plant physicians can be assumed to have been much higher. Seen against this background and the fact that large-scale production of PVC has now been going on for 45 years, the number of reported cases with (mostly ill defined) liver disease seems to be surprisingly small. Other mani-

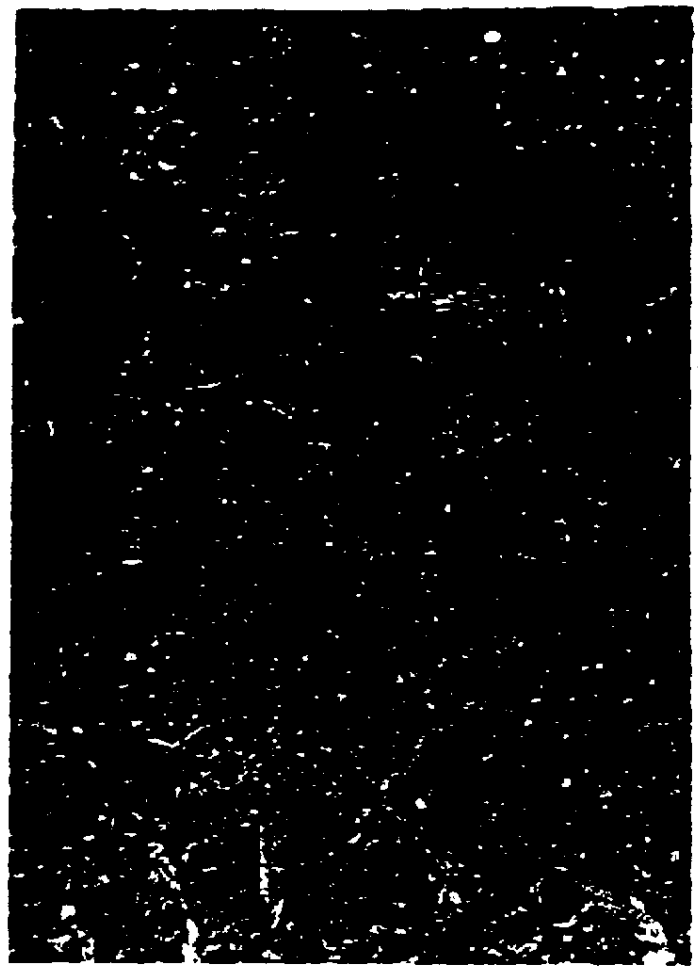

FIGURE 15. Toxic and adaptive changes of parenchyma. Conspicuous pleomorphism of littoral cells (Case no. 3; length of exposure, 18 years; biopsy 2 weeks after last exposure). H&E (×400).

festations associated with VC polymerization had been seen more frequently (acroosteolysis in 118, Raynaud's syndrome in 97, skin lesions in 40 of more than 12,000 workers). They evoked particular interest mainly between 1966 and 1971 and were thought to be restricted to avoidable manual cleaning of reactors.[a,e,w]

Thus, when we first observed evidence of liver disease of possibly occupational etiology in the workers examined, we suspected plant standards to have been particularly poor, considering that liver disease was so rarely mentioned in prior publications. Intimations made by workers seemed to confirm this assumption (distinct odor of VC vapors at diverse working areas even outside the location of reactors, deteriorating quality of ventilation after windows had been walled up, frequent symptoms of acute overexposure, and mainly manual reactor cleaning). However, with a growing number of workers examined it became evident that we dealt with a disease presenting with a multisided but predomi-

nantly inconspicuous symptomatology (for instance, minor hepatic functional insufficiency[85-88]) which, with reference to liver and spleen, even in advanced stages would be liable to escape detection if only conventional methods of examinations were employed. Therefore, statements given out by other plants that liver and spleen changes had never been observed should be met with scepticism unless proven by morphologic methods.

The dramatic discovery of cases of hemangioendotheliosarcoma of the liver in PVC workers throughout the world early in 1974 has shown that this is certainly not merely the problem of a specific plant.

None of the clinical or morphologic findings seemed to be mutually correlated nor did we find a recognizable correlation between a certain set of symptoms and length of exposure or alcohol consumption. The clustering of pathologic findings (liver, spleen, portal circulation) in this group now comprising 50 workers confirmed our previous impression[84] that we dealt with a symptomatology compatible with the diagnosis of chronic toxic liver damage,[72,73,89] similar to that seen after repeated or continuous exposure to halogenated hydrocarbons. The histomorphologic appearance of the liver was essentially characterized by *degenerative lesions* (frequently observed in chronic toxic liver injury; hyperplastic smooth endoplasmic reticulum, alterations of rough endoplasmic reticulum due to toxic derangement of membrane structures[78,109,110]), *fibrosis* (septal fibrosis or collagenization of sinusoidal walls with occasional capillarization and finally network-like interstitial fibrosis), and enlargement or *proliferation of littoral cells*.

Whereas the mostly unimpressive histologic findings permitted reflections as to possible etiology,[69,72,73,140,155] peritoneoscopic results, although usually much more suggestive of serious liver damage, could only be interpreted as unspecific evidence of injury; for instance, even pronounced capsular fibrosis merely indicates a repair stage of underlying tissue damage due to a variety of noxious agents.[30, 35, 102] Although granular to nodular surface relief in a number of cases suggested incipient derangement of lobular architecture, a final diagnosis of cirrhosis of the liver could be made only in two cases. Thus, the pathogenesis of portal hypertension with splenomegaly or of isolated splenomegaly at first remained unexplained, especially since no recognizable correlation seemed to exist between degree of hepatic lesions and degree of splenomegaly or of portosystemic collateral circulation. Liver disease in PVC workers reminds one of noncirrhotic portal fibrosis, predominantly seen in India,[16,18,116,217,126] or of so-called idiopathic portal hypertension,[20,97,98,102,103,110–112,146] respectively. In this disease entity, portal hypertension and splenomegaly are usually accompanied by similar alterations of hepatic surface and histology;[14,16,77,110,121,139,140,146] in some cases, however, portal hypertension seemed to have been the result of sclerosis or thrombosis of the portal vein.[20,97,98,102] Another analogy between liver disease associated with PVC production and noncirrhotic portal fibrosis/hypertension can be seen in the frequently observed combination of a pronounced pathologic BSP retention with other laboratory parameters being normal or only slightly aberrant;[14,20,98] BSP retention, however, can be readily explained by the character of the histologic lesions.[71] A certain resemblance to Banti's syndrome is suggested.[139,155] It should also be realized that the degree of fibrosis in our cases was most probably underrated on microscopy since surgical biopsy material, more suited for detection of fibrosis,[155] was not available. On the other hand, one should keep in mind that even the rather unimpressive alterations observed histologically (periportal and sinusoidal fibrosis, capillarization of sinusoids, degen-

erative cellular lesions) may be sufficient to explain an increase in portal pressure.[...]

In this connection, particular attention should be paid to the enlargement and proliferation of littoral cells, as described above, because of their relation to fibrogenesis.[...] Besides, proliferation of littoral cells is of diagnostic significance, indicating that the reticuloendothelial system is involved and actively participates in the process (a possibly additional pathogenetic factor in splenomegaly?). In this context, recent reports on oncogenic properties of vinyl chloride[...] should be evaluated since proliferative alterations of littoral cells are possibly the precursor stage of hemangioendotheliosarcoma. If one looks for a pattern of injury similar to that seen in VC-associated hepatic hemangioendotheliosarcoma, gross morphology, histologic appearance[...] and conjectural course of events in the pathogenesis of hemangioendotheliosarcoma occurring after exposure to Thorotrast or arsenic can perhaps serve as an example. It could be speculated that chronic stimulation of the reticuloendothelial system (possibly also of hepatocytes[...]) by a toxic substance[...] may be the common denominator.

This leads back to the question of etiology.[...] Quantitatively vinyl chloride monomer is the most likely suspect in VC-associated liver disease. Numerous hints (such as odor and acute symptoms of overexposure) contained in job histories point to the frequent release of considerable concentrations of VC at various working areas in VC polymerization,[...] even if one considers the unreliability of olfactory sensations[...] and the wide range of olfactory threshold concentrations reported in the literature.[...]

Except for Schumann's communication in 1934,[...] quoted by Williams[...] in 1959, very little is known about the kinetics and metabolism of vinyl chloride.[...] Nevertheless, considering the chemical structure of VC and the course of events in polymerization, it can be speculated that free radical mechanisms (monomer, catalysts) may be responsible for damage to cell membranes and subcellular structures (endoplasmic reticulum, "drug-hydroxylating enzyme systems"[...]), for example, by way of "lipid peroxidation."[...] Furthermore, formation of free radicals may also be involved in the oncogenic action of vinyl chloride.[...]

Regardless of such deliberations, results of animal experiments with long-term exposure to *pure VC* have demonstrated considerable hepatosplenic injury[...] apart from tumorigenesis and damage to other organs.[...] From these results it appears quite probable that the pattern of damage observed can be attributed to the effect of VC itself. It is, however, not established[...] whether and if so how far various additives[...] or intermediate compounds[...] contribute to the symptom pattern in human vinyl chloride disease.

Some comment should be made on the question of a potential health hazard for those engaged in processing the polymer to the final product. This question is even more difficult to answer and in practice of even greater importance. Detection of analogous if less pronounced lesions in some workers engaged in the manufacture of floor tiles should be reason enough also to pursue the question of possible VC-induced damage in these later stages of production. This is also suggested by the fact that VC trapped in the polymer can principally be liberated[...] during processing (e.g., calendering, moulding, extrusion, etc.) at temperatures of 100–200°C.[...] At the moment, it is also open to discussion whether PVC dust, apart from damage to the respiratory tract,[...] may cause gastrointestinal symptoms,[...] for instance, by persorption.[...]

In the future, periodic control examinations of *all* PVC workers, especially of those engaged in VC polymerization, at short intervals employing sensitive methods should be obligatory unless it should prove feasible to eliminate completely any possible air contamination.

Some of the many scientific questions connected with the problem of vinyl chloride disease may not be answerable until results of further extensive animal experiments[35,36,66,67] and of prospective and retrospective large-scale studies[29] as well as of continuous monitoring of working areas[18,105,109,144] are available.

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DISCUSSION

DR. H. BUCHTER (*University of Cologne, Germany*): It would seem better for statistical investigations on the reported liver function tests if you could compare the results with similar tests done before the workers came into vinyl chloride manufacturing. Second, in one of the two plants in Germany with incidence of vinyl chloride disease, there is much alcohol intake in the workers. Until now no liver damage has been found.

Third, in regard to low lung-function tests, we have not confirmed a pathological diagnosis at all.

There should be more discussion about the cause of this disease, i.e., whether it is vinyl chloride alone or another agent which may get together with techn al vinyl chloride, or vinyl acetate or additives. This may be important in the causation of angiosarcoma.

Last, it has been suggested that liver biopsy be done only after peritoneoscopy because of the risk of bleeding.

DR. M. L. NEWHOUSE: May I ask Dr. Lelbach how he selected his patients and how big was the exposed group he selected them from?

DR. W. K. LELBACH (*University of Bonn, Germany*): I will begin with the answer to the second part of the question. The whole group is, as far as we know, about 180 workers in this plant. We were alerted in December 1972 by Dr. Veltman's group that patients being examined for skin and bone disease also had signs of liver disease. We examined these patients.

Later we examined all patients we could bring to the clinic. It is, of course, a selected group and does not permit us to draw conclusions as to percentages.

DESCRIPTION OF MATERIAL USED FOR TESTS

Vinyl chloride (CH_2CHCl) is a colorless gas at room temperatures (boiling point, −13.9° C.). The gas has a pleasant ethereal odor and is slightly soluble in water. Its limits of inflammability are 4.0 to 21.7 per cent by volume in air.[7]

The vinyl chloride used in experiments described in this report was a commercial product having the following plant specifications: Boiling range, 95 per cent or more below −10° C. at 760 mm.; acetaldehyde, not more than 0.5 per cent; residue, not more than 0.5 per cent.

TEST APPARATUS

The test apparatus was the same as that described in a previous report dealing with ethylene oxide.[8]

COMPUTATION AND ANALYSIS OF GAS-AIR MIXTURES

The vinyl chloride-air mixtures were created by adjusting calibrated flowmeters (Venturi type) to give the desired proportions of gas and air. The vinyl chloride content was then checked by analysis.

The apparatus used was the same as that used for determining ethylene dichloride in air.[6] Briefly, the method was to subject the vinyl chloride to combustion with oxygen (explosion method using electrolytic gas to "energize" the combusiton), and absorption of the products of combustion. For mixtures containing insufficient oxygen for complete combustion, a known amount of additional air or pure oxygen was mixed with the sample before adding the electrolytic gas. A minimum amount of stopcock grease was used in the apparatus to reduce error through solubility of the gas. For the same reason rubber tubing was not used except for making joints of glass tubing, caution being taken to have the ends butt together.

TEST PROCEDURE, DESCRIPTION AND CARE OF ANIMALS

The test procedure, and the animals and their care were the same as described in the published report dealing with ethylene dichloride.[6]

RESULTS OF TESTS

The detailed test data are too voluminous to be presented in this report and only summarized results pertinent to symptoms, gross pathology, and fatality are given. Specimens of tissue were taken for microscopic examination, a report of which will be made later.

[7] See previous footnote 5.
[8] See previous footnote 6.
[9] Jones, H. W., U. S. Bureau of Mines, unpublished data.

SYMPTOMS OF ANIMALS

Control animals.—No symptoms were exhibited by the 18 control guinea pigs used in these tests or by the stock animals from which all of the test animals were taken. Also, no deaths occurred.

Exposed animals.—Table 1 gives the symptoms shown by the animals exposed to vapors of vinyl chloride and also the average period of exposure required to produce these symptoms by various concentrations of vapor in air. The reader should note that the figures in parentheses indicate that the particular symptom did not occur in the maximum period of test as given.

The highest concentration of vinyl chloride in air used in the exposures (40 per cent) exerted an almost immediate narcotic effect on the animals. Within one-fourth minute the animals fell to their sides in an apparent unconscious or narcose state, with convulsive twitchings of the trunk and extremities and jerky rapid respirations. The pigs remained in this state until death or termination of the test.

TABLE 1.—*Symptoms produced in guinea pigs during exposure to vapors of vinyl chloride*

Type of symptoms	Concentration of vapor and period of exposure producing symptoms [1]						
	40	15 to 25	10	5	2.5	1.0	0.5
Dropping to sides; incomplete narcosis; nervous phenomena; irregular twitching of extremities	½	1	2	[2] (300)	[2] (480)	[2] (480)	[2] (480)
Unsteadiness on feet; motor ataxia	[2] (10)	[2] (20)	[2] (360)	2	5	[2] (480)	[2] (480)
Apparent unconsciousness; deep narcosis; no twitching of extremities; quiet	[2] (10)	15–20	60	50	90	[2] (480)	[2] (480)
Jerky, rapid respiration	14–15	2	(3)	240	[2] (480)	[2] (480)	[2] (480)
Slow, shallow respiration	[2] (10)	20	120–360	300	300–480	[2] (480)	[2] (480)
Respirations ceased	10–20	18–35	[2] (360)	[2] (360)	[2] (480)	[2] (480)	[2] (480)

[1] Concentrations of vapor in per cent by volume; time in minutes.
[2] Not observed during maximum exposure period as given in parentheses.
[3] Not determined.

Concentrations of 10 to 25 per cent caused the animals to fall on their sides with convulsions and with jerky, rapid respirations in 1 to 2 minutes. Following this the pigs lapsed into a state of apparently deep narcosis in which the convulsive twitchings and all movements ceased, the pigs being quiet and relaxed. This occurred within 10 to 20 minutes at concentrations of 15 to 25 per cent and within 60 minutes at concentrations of 10 per cent. Slow, shallow respirations occurred with 20 minutes' exposure to 15 to 25 per cent and with 120 to 360 minutes' exposure to 10 per cent. The pigs remained in this state until death or termination of the exposure.

Concentrations of 5 and 2.5 per cent did not produce the initial symptom of "dropping to their sides and unconsciousness with convulsive twitching of the extremities." These concentrations produced first an unsteadiness in the animals, a staggering on attempt-

ing to move about, with signs of motor ataxia. This occurred within 2 to 5 minutes, and lasted 50 to 90 minutes, at the end of which time the pigs fell on their sides in an apparent profound narcosis, being entirely relaxed with no convulsions or movements of any kind. The respirations were increased in rate and amplitude, becoming

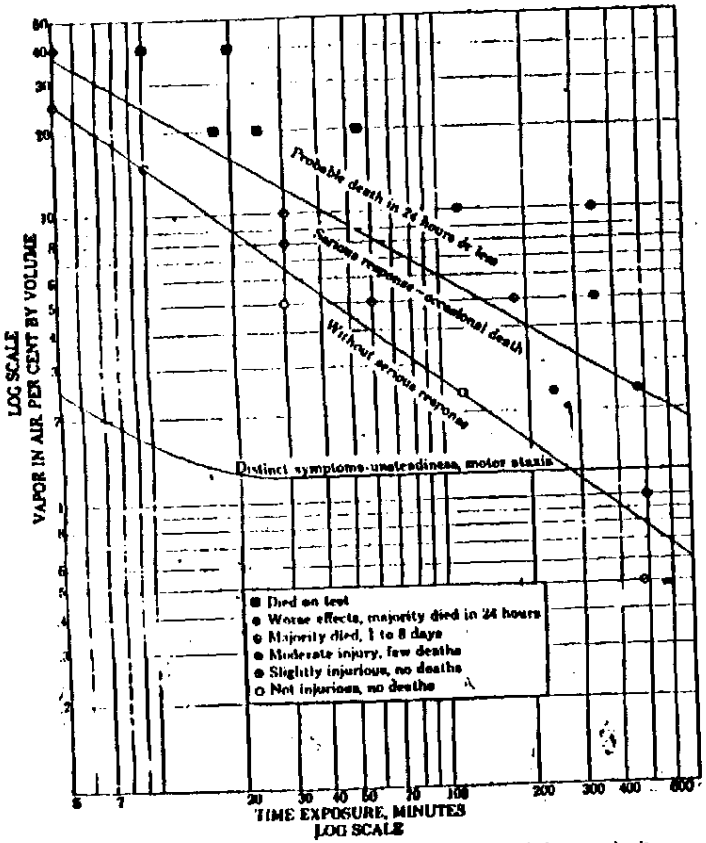

FIGURE 1.—Acute effects of exposure of guinea pigs to vinyl chloride vapor in air

rapid and jerky in character at the end of 240 minutes' exposure to 5 per cent, and slowed and became shallower at the end of 360 minutes, remaining in the latter condition until death or termination of the exposure.

Concentrations of 0.5 and 1.0 per cent did not produce any symptoms.

The general symptom of narcosis was manifested in three degrees, increasing in severity with increasing concentrations of vinyl chloride: (1) Unsteadiness, staggering, and motor ataxia; (2) incomplete narcosis in which convulsions affecting the trunk and extremities persist; (3) a state of profound or deep narcosis in which the animals are quiet, on their sides, relaxed, and without movement.

Observation showed that animals after being removed from the exposure chamber recovered from the most profound narcosis within 12 minutes.

No signs of eye or nasal irritation were observed.

SYMPTOMS EXPERIENCED BY MEN

Two of the experimenters were exposed to 2.5 per cent vinyl chloride in air for a period of approximately three minutes. They reported that the gas had a fairly pleasant odor. They soon began to feel dizzy and disoriented as to space and size of surrounding objects, and complained of a burning sensation in the soles of the feet. They immediately recovered on leaving the chamber and complained only of a slight headache, which lasted about 30 minutes.

GROSS PATHOLOGY

Control animals.—A total of 18 control animals were killed for autopsy. No gross pathology resembling that found in the exposed animals was found. Also no deaths occurred among the control animals.

Exposed animals.—The gross pathological changes found in the animals that died during exposure (see fig. 1 for conditions of exposure causing death on test) were intense congestion and edema of the lungs and a hyperemia of the kidneys and liver. The lungs were light pink in color; the cut section was uniformly light red, and bled freely. A frothy exudate was present in the large bronchi, and squeezing of the lung tissue covered the cut surface with a frothy, bloody fluid. The kidneys and liver were deep red to purple in color and the cut sections were moist and dripped blood.

The animals that died within 1 to 8 days following exposure showed a congestion and edema of the lungs, with a swelling and hyperemia of the kidneys. The findings in animals of these same groups which were killed for autopsy immediately after exposure showed a hyperemia and edema of the lungs, with a congestion of the liver and kidneys. Animals that were killed for autopsy 4 days following exposure still showed a hyperemia with areas of congestion throughout the lungs, whereas those killed for autopsy 8 days following exposure showed atelectatic and emphysematous patches throughout the lungs.

The findings in those animals that were killed immediately after exposure to conditions that did not cause death, but which caused

a mild degree of pathological change, were principally congestion and slight edema of the lungs, and hyperemia of the liver. The findings in the lungs were not as severe as noted in the exposures previously described. These changes cleared up in most of the animals within 8 days after exposure.

A clouding and thickening of the cortex of the kidneys was noted in those animals killed immediately after exposure to 25 per cent for 5 minutes and 5 per cent for 1 hour. This change was not noted in members of those groups killed 4 days and 8 days later.

No significant gross pathological changes were found in animals exposed to 15 per cent for 10 minutes, 5 per cent for 30 minutes, and 2.5 per cent for 2 hours.

DISCUSSION OF PATHOLOGY

Vinyl chloride is irritating to the lungs. Congestion and edema of the lungs are the most constant and prominent observations for exposure to conditions which caused death during or following exposure. Accompanying the lung changes was a passive congestion of the liver and kidneys.

The signs of lung irritation which were found immediately after exposure to conditions which did not cause death, practically disappeared within 8 days. A clouding and thickening of the cortex of the kidney was noted immediately after exposure to 25 per cent for 5 minutes and 5 per cent for 1 hour. These kidney changes were not present in animals of the same groups after 4 days.

FATALITY AND SUMMARY OF PHYSIOLOGICAL RESPONSE

A summary of the fatality and response of guinea pigs exposed to various concentrations of vinyl chloride in air is shown graphically in Figure 1, and given in conventional degrees of response in Table 2. The results of each experiment are designated by a symbol which represents one of six different degrees of severity. With the exception of concentrations causing death during exposure for which the results obtained for individual animals are given, the selected symbol describes the results obtained for at least one-half the individual animals, and in most cases the results are for the majority of a group (at least three and usually six animals) exposed to a given condition.

It will be noted from the legend on Figure 1 that the six degrees of response are—

1. Died on test.
2. Majority died within 24 hours.
3. Majority died, 1 to 8 days.
4. Moderate injury, few deaths.
5. Slightly injurious, no deaths.
6. Not injurious, no deaths.

In addition to representing the response of each group by symbols, the latter have been separated into four general fields or zones of probable response, namely,

1. Probable death, 24 hours or less.
2. Serious response, occasional death.
3. Without serious response.
4. Distinct symptoms.

Table 2 gives the concentrations which produce the degrees of response generally reported in the literature dealing with noxious gases. These data may be compared with toxicological data for other compounds. [1] [4] [5] [6] [7] [9] [10] [11]

TABLE 2.—*Acute effects of exposure of guinea pigs to vinyl chloride in air*

Effects of exposure after various periods of time	Concentration, per cent by volume
1. Kills in a very short time	20 to 40
2. Serious symptoms in a very short time	10
3. Moderate symptoms in a very short time	2.5 to 5
4. Dangerous in life in 30 to 60 minutes	10
5. Marked symptoms in 30 to 60 minutes	5
6. Maximum amount for 60 minutes without serious disturbance leading to death	3 to 7
7. Maximum amount for 60 minutes without marked symptoms	1.0 to 1.5
8. Maximum amount for several hours without serious disturbances	0.5
9. Maximum amount for several hours with but slight or no symptoms	1.0

CAUSE OF DEATH DURING AND FOLLOWING EXPOSURE

The animals exposed to 20 to 40 per cent vinyl chloride entered a state of profound narcosis which terminated in death. Recovery was rapid and without fatality following exposure for periods less than those causing death during exposure. This indicated that the degree of lung irritation acquired in these relatively short periods was insufficient to cause death. With concentrations in the range of 5 to 10 per cent the period between a profound but nonfatal narcose state and death was much longer, and permits considerable lung irritation to take place. Also, there was a probable action of vinyl chloride or products of its decomposition on the liver and kidneys. With 2.5 per cent, profound narcosis was present after 90 minutes and irritation of the lungs occurred after several hours, but death was exceptional.

[1] [4] [5] [6] [7] [9] [10] See previous footnotes 3, 4, 5, 6.

[11] Cotton, R. T., and Young, H. D.: The use of carbon dioxide to increase the insecticidal efficiency of fumigants. Proc. Entomological Soc. of Washington, vol. 31 (1929), pp. 97-102.

[4] Sayers, R. R., Yant, W. P., Thomas, B. G. H., and Berger, L. B.: Physiological response attending exposure to vapors of methyl bromide, methyl chloride, ethyl bromide, and ethyl chloride. Pub. Health Bul. No. 185 (1929), 36 pp.

[9] International Critical Tables, first edition (1927), vol. 3, p. 318. Also see errata sheet, vol. 7.

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HEALTH HAZARDS FROM VINYL CHLORIDE

With regard to symptoms and pathology, as well as the effecting concentrations, the response of guinea pigs to vinyl chloride appears to be similar to their response to ethyl chloride.[8] In equal concentrations and for single exposures, vinyl chloride is less harmful than gasoline, benzene, chloroform, and carbon tetrachloride.

The comparatively harmless response to concentrations of vinyl chloride that will maintain a narcose state, together with its rather pleasant odor, suggests a possible use for producing surgical anaesthesia. This could be produced quickly by high concentrations and maintained with lower concentrations. Much additional work is necessary, however, to ascertain the practicability of its use.

Vinyl chloride does not possess adequate warning properties of the odor or irritation type. With concentrations of 5 per cent or less, however, it gives warning by producing symptoms of dizziness and disorientation in advance of harm. With higher concentrations the narcotic action is very rapid and persons would have little time to heed the warning symptoms before helplessness would ensue.

Vinyl chloride boils at less than ordinary room temperatures. As a rule, it is contained in cylinders under pressure. This is conducive to escape of the gas; on the other hand, the high concentrations required to produce physiological harm minimize the danger from leakage. There is, in fact, more danger from explosion than from harm to health from exposure.

ACKNOWLEDGMENTS

The writers desire to give acknowledgment to J. G. Davidson, manager of chemical sales for the corporation mentioned, and E. W. Reid, senior fellow of this firm's fellowship at the Mellon Institute, Pittsburgh, Pa., for sponsoring the investigation, to R. R. Sayers, chief surgeon, Bureau of Mines, for suggestions and advice, and to H. F. Brubach, laboratory assistant, Bureau of Mines, for assistance in performing the experimental work.

SUMMARY AND CONCLUSIONS

The acute physiological response of guinea pigs to air containing vinyl chloride was determined. The concentrations of vapor and periods of exposure ranged from those which produced death to those which caused no apparent effect after several hours' exposure. The symptoms, gross pathology, and fatality are given with a discussion of potential hazards.

1. The symptoms are principally those of narcosis. They range from unsteadiness and motor ataxia to incomplete and, finally, complete narcosis. The respirations vary from a rapid, jerky type accompanying the beginning of narcosis to a later, slow, shallow type.

2. The principal gross pathological findings were congestion and edema of the lungs, with hyperemia of the kidneys and liver.

3. Exposure to 20 to 40 per cent kills guinea pigs in a very short time; 10 per cent is dangerous to their lives after 30 to 60 minutes' exposure; and 0.5 per cent is the maximum allowable amount for several hours without acute disturbances of a serious nature.

4. With regard to relative toxicity (concentrations causing acute harm), vinyl chloride is less harmful than carbon tetrachloride and chloroform, and is similar to ethyl chloride.

5. The danger from explosion exceeds the health hazard from exposure.

6. Vinyl chloride does not possess adequate warning properties of the odor or irritation type. It gives warning, however, by producing symptoms of dizziness and disorientation in advance of harm, except when present in exceedingly high concentrations which would cause almost immediate helplessness and unconsciousness.

7. The narcotic action of vinyl chloride and its comparatively low toxicity suggest its possible use for surgical anaesthesia.

[8] See previous footnote 8.

DEATH RATES IN A GROUP OF INSURED PERSONS

Rates for Principal Causes of Death for June and First Six Months of 1930

The accompanying tables are taken from the Statistical Bulletin for July, 1930, issued by the Metropolitan Life Insurance Co. They present the mortality record of the industrial insurance department of the company for June, 1930, as compared with the preceding month and with the corresponding month of last year, and also give the rates, by white and colored policyholders, for the first six months of the years 1928, 1929, and 1930. Death rates are given for the principal causes of death, and are based on a strength of approximately 19,000,000 insured persons.

It should be remembered that these rates apply to a more or less selected group of persons. In recent years the general death rate for this group has been approximately 73 per cent of the rate for the registration area of the United States.

JUNE, 1930

The death rate for June among these persons was 8.3 per 1,000, the same as for June of last year, and the lowest rate for the month in the mortality records of the company.

As compared with June of last year, improvement is noted for diphtheria, influenza, tuberculosis, pneumonia, accidents, and homi-

Mutation Research, 57 (1978) 226—234
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CHROMOSOMAL ANALYSES IN VINYL CHLORIDE-EXPOSED WORKERS

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(Received 1 November 1977)
(Accepted 30 January 1978)

Summary

Chromosomal morphology from cultured peripheral lymphocytes was studied in 81 men; 57 of the men were employed on plants manufacturing vinyl chloride or polyvinylchloride, 19 were on-site controls and 5 were off-site controls. There was a significant increase in chromosomal abnormalities in the exposed workers when compared with the controls. The greatest statistically significant increase in total B and total C cells occurred in autoclave operators, with smaller increases in other job categories. The increase in chromosomal aberrations was correlated with the length of exposure and with a history during the year prior to sampling (1973—1974) of exposure to excursion levels of vinyl chloride. Information on smoking habits was obtained 18 months after blood sampling and a positive correlation between these and total C cell abnormalities was found. There was no positive correlation with various other parameters (bilirubin, platelets, γ-glutamyltranspeptidase, alkaline phosphatase, alanine transaminase and aspartate transaminase). It was not possible to estimate which of the three parameters (smoking history, length of employment or exposure to excursion levels) was the most important.

Introduction

Vinyl chloride has been shown to be carcinogenic in experimental animals [11] producing tumours of various types including hepatic angiosarcoma.

Epidemiological studies have confirmed that workers exposed to vinyl chloride have a higher incidence of hepatic angiosarcoma than an unexposed population [3,9].

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl transpeptidase; PVC, polyvinylchloride; VC, vinyl chloride.

As many carcinogens have mutagenic effects several studies on human lymphocytes have been undertaken to ascertain whether vinyl chloride produces somatic mutations. In two of the reports a total of 20 workers were examined and an increase in chromosomal aberrations in vinyl chloride-exposed workers was noted [6,5]. The report by Kilian et al. [10] described the examination of 121 workers from a vinyl chloride production plant and no increase in the level of abnormalities was found when compared with pre-employment examination. In a preliminary report of out work the results of a controlled examination of men on vinyl chloride production and polymerisation plants were described [14,15] and an increase in chromosomal abnormalities was reported. We now report the results of chromosomal analyses on the men and the correlations between those results and various occupational and biochemical parameters.

Methods

Samples

Blood samples (10 ml) were taken into heparinized tubes. Cultures of peripheral lymphocytes were prepared using the standard Difco kits (Difco Laboratories, Detroit, Mich., U.S.A.) by incubating the lymphocytes with phytohaemagglutinin at 37°C for 48 or 72 h. The slides prepared from these cultures were coded before scoring to ensure unbiased analyses. 50 cells from each of the 48- or 72-h cultures from each individual were analysed (except for one person in whom 100 cells from each culture were analysed). The abnormalities observed were classified using the method of Buckton and Pike [2] but cells with less than 45 chromosomes were excluded.

This classification defines B cells as cells with either a chromatid break or gap or a chromosome gap. C cells are cells with larger chromosomal abnormalities and are subdivided into those considered as unstable (Cu cells) including cells with dicentric or ring chromosomes or fragments, and those considered as stable (Cs cells). Cs cells have translocations or inversions but cells with inversions which were a constitutional abnormality were excluded. Translocations were determined by assessment of centromeric position.

History

Blood sampling was carried out in July 1974 and at the same time each subject was asked for a medical and occupational history, which was recorded on a questionnaire. Subjects with recent history of exposure to X-rays, prolonged drug treatment or recent viral infections were excluded from the study. Any experience in the period July 1973—July 1974 of exposure to vinyl chloride for short-term excursions which could be detected by smell and the description of the type of occupation were recorded. Further information on length of service and occupation was obtained from personnel records.

Occupation

The population examined consisted of 57 workers employed on plants manufacturing vinyl chloride (VC) or polyvinylchloride (PVC), 19 on-site controls and 5 off-site controls. The 57 VC/PVC workers were classified into 6 groups (see Table 1). Group 1 consisted of 17 PVC autoclave workers who

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operated and cleaned the autoclaves; Group 3 of 10 men involved in drying and packing the PVC powder; Group 3 of 7 men involved in the production of VC; Groups 4 and 5 consisted of engineering maintenance men for PVC (11 men) and VC (7 men) equipment and plant, and Group 6 of 5 men with various occupations in the VC/PVC plant other than process operators. The on- and off-site controls were combined into a single control group of 24 men, because no significant difference between them was observed. This classification is more detailed than that used for the previous reports [14,15] and now includes 81 samples. An assessment of the atmospheric levels of VC to which these men were exposed has been made [1] and this provides the best data available on average exposure levels for autoclave workers, who by virtue of their jobs are likely to be exposed to the highest average levels of VC. The estimated average operator exposure to VC on PVC plants was:

1945—1965	approx.	1000 ppm
1955—1960	approx.	400—500 ppm
1960—1970	approx.	300—400 ppm
Mid 1973	approx.	18 ppm
1975	approx.	5 ppm

Smoking history

About 18 months after the blood samples were taken, it was decided to examine the effect of smoking history on chromosomal aberrations and, therefore, the smoking history was obtained from the men. Questionnaires on current smoking habits, historical smoking habits and the quantity smoked were completed.

Liver function tests

During the medical surveillance of vinyl chloride-exposed workers, blood samples were analysed for bilirubin and the following enzymes: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT). Platelet counts were also performed and the results have been included under liver-function tests. The off-site controls did not undergo liver-function tests.

Statistical analysis

As the number of variables measured was so large, a subset had to be selected for analysis. To aid this selection process, correlation coefficients were calculated between each chromosomal abnormality and each quantifiable occupational variable. Equations relating the selected chromosomal variables to the other variables were then fitted by multiple linear regression. Qualitative variables, such as recent high exposure, were included in these equations by using dummy variables as described by Davies and Goldsmith [4]. To include smoking information in the study, a further selection had to be made from the set of possible smoking variables.

Tests for statistical significance were carried out using Student's "t" test. As the chromosomal abnormality variables were clearly not normally distributed, an additional analysis treating them as a Poisson distribution was carried out on a Generalised Linear Model programme [12].

TABLE 1

RESULTS OF CHROMOSOMAL ANALYSES IN WORKERS EXPOSED TO VINYL CHLORIDE AND CONTROLS

Group	Number	Average duration (years)	Average age (years)	Number of cells	Chromatid gaps	Chromosome gaps	Chromatid breaks	Total B cells
1 Autoclave operators	17	10.7	41	1700	5.94 [a] 1.41	0.47 0.21	0.88 0.21	6.88 [b] 1.18
2 Dryers and packers	10	12.7	42	1000	4.40 [a] 0.67	0.60 0.26	1.00 0.33	6.00 [b] 0.61
3 VC operators	7	6.3	44	700	4.71 [a] 0.86	0.43 0.20	0.71 0.29	5.14 [b] 0.67
4 PVC maintenance operators	11	18.5	47	1200	5.48 1.48	0.32 0.27	0.64 0.28	6.83 1.48
5 VC maintenance	7	6.1	36	700	6.57 [a] 1.88	0.71 0.42	0.71 0.18	7.86 1.67
6 Miscellaneous	5	8.6	40	500	5.00 [a] 0.84	0.0 0.0	0.80 0.37	5.40 1.12
C Controls	24	0	44	2400	2.71 0.44	0.62 0.15	0.50 0.18	3.21 0.42

[a] Greater than control at 5% level of significance.
[b] Greater than control at 1% level of significance.
The upper figure in each row is the mean and the lower figure is standard error.

The results of the chromosome analyses have been expressed as either (a) the number of abnormalities per 100 cells or (b) when totals are referred to, as the percentage of abnormal cells. The former may provide an overestimation because more than one abnormality may occur in a cell. In this study, however, no cell contained more than 1 ring or dicentric. Statistical correlations and significance estimations have been made using both methods of expressing the data.

Results

The results of analyses from 48- and 72-h cultures were not significantly different and the data have been pooled in Table 1 for further analyses. The average ages of the workers in the various groups are similar.

The number and percentage of chromosomal abnormalities, classified according to Buckton and Pike [2], are shown in Table 1. For the majority of the abnormalities the value for the control group is lower than the value in any of the exposed groups; the exceptions are for chromosome gaps, where the control value is relatively high, and for fragments, where the control value is higher than the value of Group 6 but lower than the value in other groups. The group with the greatest number of significantly increased values is Group 1 (autoclave workers), where the values for total B cells, total Cu cells and total C cells are significantly higher than the control values ($p < 0.01$). Of the other 5 groups, Group 5 (VC maintenance) has the highest values, and Group 6 (mis-

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Chromatid gaps	Chromosome gaps
.94 [a]	0.47
.41	0.21
.40 [a]	0.80
67	0.25
71 [a]	0.42
86	0.20
45	0.32
45	0.27
37 [a]	0.71
38	0.42
00 [a]	0.0
34	0.0
71	0.62
14	0.16

Chromatid breaks	Total B cells	Fragments	Dicentrics	Rings	Total Cs	Total Cs	Total C cells	Total abnormal cells (chromatid breaks + total C cells)
0.88	6.59 [b]	1.82 [b]	0.47	0.06	1.82 [b]	0.47	2.29 [b]	3.16 [b]
0.31	1.16	0.43	0.24	0.05	0.34	0.21	0.43	0.87
1.00	6.00 [b]	0.80	0.30	0.10	1.00	0.40 [a]	1.40	2.40
0.33	0.61	0.29	0.21	0.10	0.39	0.16	0.45	0.86
0.71	5.14 [a]	1.57	1.00	0.0	1.43 [a]	0.29	1.71 [a]	2.43 [b]
0.29	0.67	0.65	0.44	0.0	0.30	0.16	0.36	0.58
0.64	5.22	1.37 [a]	0.64 [a]	0.09	1.45 [a]	0.32	1.68 [a]	2.32
0.25	1.46	0.36	0.30	0.09	0.41	0.18	0.51	0.69
0.71	7.86	1.14	0.71	0.0	1.57 [a]	0.14	1.71 [a]	2.43 [b]
0.15	1.87	0.40	0.29	0.0	0.37	0.14	0.43	0.57
0.80	5.40	0.0	0.20	0.20	0.40	0.20	0.60	1.40
0.37	1.12	0.0	0.20	0.20	0.40	0.20	0.40	0.75
0.50	2.31	0.42	0.21	0.0	0.50	0.05	0.55	1.05
0.15	0.42	0.16	0.06	0.0	0.12	0.05	0.12	0.26

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cellaneous) the lowest with only chromatid gaps occurring significantly more frequently than in the controls ($p < 0.05$). The remaining 3 groups have values which are intermediate between Groups 5 and 6.

When the results from those with a history of exposure to excursion levels of VC are tabulated separately from those without such a history, it can be seen that those with a history of short-term exposure have a higher percentage of abnormal cells (Table 2).

In Table 3 the correlations at various levels of significance of chromosomal

TABLE 2

THE INFLUENCE OF A HISTORY (1973–1974) OF EXPOSURE TO EXCURSION LEVELS OF VC ON THE PERCENTAGE ABNORMAL CELLS [a]

Group	History of recent exposure			No experience of excursion			Total		
	n	Total B	Total C	n	Total B	Total C	n	Total B	Total C
1	9	8.00	2.67	8	5.00	1.88	17	6.59	2.29
2	—	—	—	10	6.00	1.40	10	6.00	1.40
3	—	—	—	7	5.14	1.71	7	5.14	1.71
4	5	8.20	2.60	6	3.83	1.00	11	5.82	1.86
5	3	8.00	1.67	4	7.75	1.75	7	7.86	1.71
6	2	7.50	1.00	3	4.00	0.17	5	5.40	0.60
C	—	—	—	24	2.21	0.58	24	2.21	0.58

[a], number of workers; Total B, mean percentage of B cells; Total C, mean percentage of C cells.

TABLE 3

CORRELATIONS BETWEEN LENGTH OF EMPLYMENT AND CHROMOSOMAL ABNORMALITIES

Occupational factor	Chromosomal aberrations correlated at 1% significance or 5% significance	
Length of employment	Chromatid gaps	Dicentrics
	Total B cells	Rings + dicentrics
	Fragments	Total Cu cells
	Total C cells	
	Total Cs cells	

All correlations are positive.

aberrations (both specific abnormalities and the classifications used in Table 1) with occupational history (length of employment) are presented. All correlations are positive.

The highest correlation is between the length of the employment and chromatid gaps, fragments, total B cells, total Cs cells and total C cells. From a consideration of these correlations and the distributions of the chromosomal data, chromatid gaps, total C cells and fragments have been selected as being the most informative measurements from the statistical point of view for further statistical analyses.

If the variable for exposure to excursion levels, which was determined from the occupational history, is added to the analysis, it is found that both it and the length of employment are significantly correlated with chromatid gaps, total C cells and fragments. As the length of exposure and experience of recent exposure to short-term excursion are themselves positively correlated, it is impossible to estimate the relative effects of these two variables with any great confidence. The correlations between liver-function tests and chromosome aberrations are shown in Table 4. All are negative at either the 5% or 10% significance level. When the variable for higher short-term exposure is intro-

TABLE 4

CORRELATIONS BETWEEN LIVER-FUNCTION TEST RESULTS AND CHROMOSOMAL ABERRATIONS

Liver function test	Correlation with chromosomal aberrations at 5% significance	or 10% significance
ALT	Total B cells	Chromatid gaps
	Total C cells	Dicentrics
	Total Cu cells	Rings + dicentrics
AST	—	—
ALP	Total C cells	Total B cells
GGT	Total Cs cells	—
	Total B cells	
Bilirubin	—	—
Platelets	—	Chromosome gaps

All correlations are negative.

duced there is no correlation between the remaining variation in any chromosomal aberrations and liver-function tests.

There was an interval of 18 months between blood sampling and obtaining the smoking history. It has been assumed that the smoking history obtained in this way adequately reflected smoking habits at the time of blood sampling. A list of variables can be derived from the smoking history. Type of smoking, smokers versus non-smokers, duration of smoking, total amount of tobacco smoked per week and historical smoking habits are variables each of which might be thought important. The multiple linear regression programme was used to select the most significant correlations, and, although quantity currently smoked was positively correlated with total C cells ($p = 0.025$) and with total Cu cells ($p = 0.05$), the largest correlation was found to be between present smoker versus present non-smoker and total C cells.

The individuals' percentage values of C cells in relation to length of employment, experience of higher short-term exposure and smoking habits are given in Table 5. The mean values of percentage of C cell abnormalities in those not exposed to VC was 0.58, increasing to 1.59 in those exposed for up to 10 years and to 1.92 in those exposed for greater than 10 years. The mean value for present smokers, irrespective of their occupational history, was 1.80 and for non-smokers was 1.06. The mean value for those employed in VC/PVC manufacture with experience of higher short-term exposure (2.29) was higher than for those without such exposure (1.45). This tabulation illustrates that these three factors are associated with an increase in the percentage of C cell abnormalities. As an alternative the results were assumed to conform to a Poisson distribution and the Generalised Linear Model programme was used for

TABLE 5

TABULATION OF INDIVIDUALS' PERCENTAGE C CELLS WITH THREE OTHER PALAMETERS

	Years of employment			
	0 (Controls)	1—10	10	Average
Present non-smoker				
Recent		0, 2, 1, 2, 2	0, 2, 2	1.04
No recent	1, 2, 1, 1, 0, 0, 0 0, 0, 1, 1, 1, 2	0, 0, 0, 1, 0, 2, 0	0, 2, 2, 0, 2, 2	
Present smoker				
Recent		1, 2.5 [a]	2, 2, 7, 2, 0, 2	1.80
No recent	1, 0, 0, 0, 0, 1, 1, 0	1, 2, 1, 2, 5, 1, 2, 2, 4, 1, 4, 2, 0	2, 2, 2, 1	
No smoking history				
Recent		2	2, 6	1.21
No recent	0, 1, 0	1, 2, 0, 2, 0	0, 0, 0	
Average	0.58	1.59	1.92	

Average for those with a history of exposure to excursion levels: 2.29.
Average for those exposed with no history of exposure to excursion levels: 1.45.
Recent, experience of exposure to excursion levels of VC in the period June 1973—July 1974.
No recent, no experience of exposure to excursion levels of VC in the above period.
[a] Mean value from a count of C cell abnormalities in 300 cells.

equation fitting. The duration of employment variable was found to be significant at the 5% level, the present smoking variable was significant at the 10% level and the history of exposure to excursion levels was not significant. As these variables were not completely independent of one another, too much reliance cannot be placed on these estimates of relative importance.

Discussion

The relationship between the level of chromosomal abnormalities and the various factors which influence their level is complex. There are 4 factors which have been shown to be associated with increased chromosomal abnormalities in these VC/PVC workers: the job category, the length of employment and experience of exposure to short-term excursion levels of VC and smoking habits.

The autoclave workers (Group 1) had the largest number of categories of abnormalities which were significantly different from the controls (Table 1). The only group which had values similar to those of controls was Group 6 which consisted of laboratory workers and managers. The autoclave workers are considered to have had the highest exposure to VC and those in Group 6 were in jobs which gave them infrequent or low-level exposure. It seems, therefore, that the overall exposure level has an influence on the level of abnormalities.

Killian et al. [10] reported no increase in chromosomal abnormalities in VC workers who were not involved in the polymerisation process. Our Group 3 probably corresponds most closely with their results. A direct quantitative comparison is not warranted, however, because so many factors may differ in the two studies (e.g. exposure levels, chromosomal-analysis techniques). In particular the job carried out by, and thus the exposure of, individual workers with similar job titles differs between countries and even between plants in the same country.

The length of employment was positively correlated with the level of abnormalities and this effect was demonstrated in Table 3. This finding contrasts with that of Funes-Cravioto et al. [6], who suggested that their recently employed workers had the highest chromosomal abnormality rate. The difference may be the result of other factors, such as a history of exposure to excursion levels and smoking habits, which were not recorded in the study reported by Funes-Cravioto et al. [6].

Those workers with an experience of higher short-term exposure had higher chromosomal abnormality values than those without such a history (Tables 2 and 5). This influence cannot explain why the exposed group values were higher than the controls because Groups 2 and 3 (dryers and VC operators), which did not contain individuals with experience of recent short-term exposure to excursion levels, have statistically significant increases in abnormalities.

There was a significant correlation between the smoking habits and the total C cells. The smoking data can be criticised because the questionnaire was completed so long after the blood samples were obtained. No accurate data on smoking habits at the time of blood sampling were obtained and thus the correlation had to be based on the available data on smoking, which could be con-

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sidered less satisfactory because they were obtained 18 months after sampling. Nevertheless, it seems likely that smoking does have an influence on chromosome abnormalities in VC exposed workers, although the effect is, if anything, reversed in the control group.

The statistical analysis is complicated by the inter-relationships between the 4 variables (job category, length of employment, experience of recent short-term exposure to excursion levels and smoking history). This difficulty is exemplified in Table 5, where three of these variables are shown to influence the level of C cell abnormalities.

There is no correlation between chromosomal aberrations and liver-function tests. This is not surprising as such significant differences as were found in the data on liver-function tests between 600 workers exposed to VC and 200 controls (G.M. Paddle, unpublished observations) would not be found in these much smaller samples.

One further point of interest is that the most informative parameters in detecting damage to chromosomes due to VC are total C cells, total Cs cells, total B cells, chromatid gaps and fragments. This suggests that VC produces a random effect in all categories of abnormality. The biologically-significant abnormalities could be considered to be the total Cs cells or the total of cells showing ring and dicentric forms of chromosomes. Nevertheless, if further studies on chromosomal aberrations in VC workers are undertaken, the total C cells is the abnormality which would be of most value from a biological and statistical viewpoint.

The greatest significance of mutagenic effects to the exposed person and the community lies in the possibility that the mutational event may occur in the germ cells and be transmitted to the next generation. If chromosomal aberrations occur in germ cells one sequela which may occur is the induction of dominant lethal mutations. Levels of VC as high as 30,000 ppm in the inspired air produced no dominant lethal mutations in mice (Anderson et al., 1976), suggesting that the active metabolites of VC may never reach the testis and germ cells or if it does it is not metabolised. In man, a germ-cell effect resulting in a dominant lethal mutation would be observed as foetal loss. Infante and his colleagues [7—9] have described a study in which the history of foetal loss of wives of workers exposed to VC is compared with that of a control group. Apart from the inaccuracies inherent in a retrospective survey of this type and the assumption that the increase in foetal loss is due to a mutational event, the statistical methods have been criticised [13]. Further, carefully controlled studies will be necessary to establish whether VC induces dominant lethal mutations in man.

An increased level of chromosomal abnormalities may result from high exposure to VC, but the considerable overlap in values observed between various groups in this study suggest that exposure of an individual cannot be predicted accurately from a single chromosomal analysis. The data from chromosomal analysis of groups of workers do differ significantly from that of controls, suggesting that the greatest reliance should be placed on group data.

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Mutation Research,
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CHROMOSOME
ACETATE EXP(

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(Received 29 / :pter
(Revision received 2
(Accepted 6 Februa

Summary

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