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

H. J. Marsteller and W. K. Leibach

Medizinische Universitätsklinik
D-53 Bonn, Federal Republic of Germany

R. Müller and P. Gedigk

Pathologisches Institut der Universität Bonn
D-53 Bonn, Federal Republic of Germany

INTRODUCTION

Economic Considerations; Technology

As early as 1833[68] and 1838,[44] 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)[101] and organic peroxides were used for catalyzing VC polymerization (Klatte and Rollett, 1914).[68] In 1928, PVC production was started in the United States and in 1933 in Germany.[44] The enormous growth of VC and PVC production capacities over the past 45 years ran parallel to the rising economic importance of plastic materials[27] (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).[28,51] Total sales of PVC amounted to 850,140 German marks in 1972.[28] 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).[114]

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.[68] Thus, industries that manufacture the end product operate on a much larger scale than those producing the polymer, but the companies are often identical.[51,61]

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.[27] 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).[2,3,8,27,101] 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)[27,28,65]

	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)[82] 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.[81] 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.[101] 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

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amounts of acid (free HCl), acetaldehyde, iron, acetylene, butadiene, water, and stabilizers.[101] Avoiding impurities is a prerequisite since they retard polymerization.[81,101] Liquid VC is stored and transported in steel containers.[5,81,101] 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.[101]

Four *methods of polymerization* are used for industrial fabrication of polyvinyl chloride: emulsion, suspension, bulk, and solvent polymerization.[5,6,81,85,81] Commercially most important were the two older methods of emulsion and suspension polymerization, but now bulk polymerization has been added.[85] 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.[27] Initiation of polymerization is accomplished with compounds that form free radicals at relatively low temperatures,[4] 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.[4, 5, 65] Formation of free radicals also occurs by thermal decomposition of peroxide bonding (—O—O—).[44] 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.[4, 44, 81, 87, 133] 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[27] 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.[4–6,65] 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.[4] 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*

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(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.[45,65,132]

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[80,107,127,128] and problems of occupational health[104] were investigated. At first, vinyl chloride appeared to be a suitable narcotic which, even after Oster in 1947[100] and Carr in 1949[25] had observed severe cardiac arrhythmia (believed to be due to potentiation of adrenaline effect[70]), was considered to be one of the least dangerous chlorinated hydrocarbons.[24,70,83,99,129]

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.*[148] 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,[40] Parmeggiani,[103] and Hervieux and Tessier[66] between 1953 and 1959. Acute intoxication was again reported, this time in Great Britain, with acute collapse during VC polymerization[90] and a second degree burn after direct contact with vinyl chloride.[62] Filatova *et al.*[53,54] 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[27] 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 168 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 3. 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.*[55] again reported on a Raynaud-like syndrome and central nervous system symptoms in PVC workers. Pushin[113] 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

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"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.*[32] 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,[26] Marin *et al.*,[59] Bourrichon,[20] Wilson *et al.*,[150] and Harris Adams.[63] With this clustering of publications the disease became known as "occupational acroosteolysis" with typical roentgenologic findings,[26] 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").[31,42] Between 1969 and 1972, Anghelescu *et al.*,[7] Filatova and Antonyuzhenko,[50] Dinman *et al.*,[31,42,43] (on the basis of a large-scale epidemiologic study), Lefèvre,[82] Markowitz *et al.*,[90] and Dugois *et al.*[48] 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[61,62,81,99,150,163]). Single deviant observations made in 1970 by McCord[94] and by Misgeld *et al.*[96] in 1973 as well as warnings voiced in the past by Tribukh *et al.*[148] in 1949 and by Danishevskii *et al.*[30] 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,[9,40,60,61,67,89,115,159] apart from the minimal risk attributed to VC inhalation[52, 69, 70, 81, 89, 135, 153] (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.*[54]) themselves. The experiments of Maltoni *et al.*[58] 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.[151,152] However, results published by Torkelson *et al.*[147] 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.[64] 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.[73] 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."[79]

LIVER DISEASE IN PVC WORKERS

Clinical Observations; General Outline

It seems quite remarkable that after the findings of Tribukh *et al.*[148] 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 angioscarcoma 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 Flucher (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	2,582	118	97	40	73	5 Acute intoxications
	86 + *x*						3 Fatalities
	12.724						

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* —, 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.

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§ 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.

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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 hemorrhage and edema
	m (5) r (5)	200,000	30 min	Deep narcosis (1 mouse dead)	Liver: congestion,

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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.

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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

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	r (30)	20,000		in appearance	Spleen/kidney: no differences between control and experimental animals 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

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
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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 hemorrhage and edema
	m (5) r (5)	200,000	30 min	Deep narcosis (1 mouse dead)	Liver: congestion, partly fatty infiltration (r)

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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)	200	4 h/d	Normal in appearance, mortality, and growth	Liver: average weight increase
	r (5)		2 h/d for 6 mo		
	r (5)		1 and 0.5 h/d for 6 mo	"Entirely normal"	
	r (5)				
		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
	(same procedure as in 200 ppm)				
	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	8 h/d for 2 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
		80,000	8 h/d for 13 d		
	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

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	r (30)	20,000	[illegible]	in appearance	Spleen/kidney: no differences between control and experimental animals 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

					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

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.[65,136,162]

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

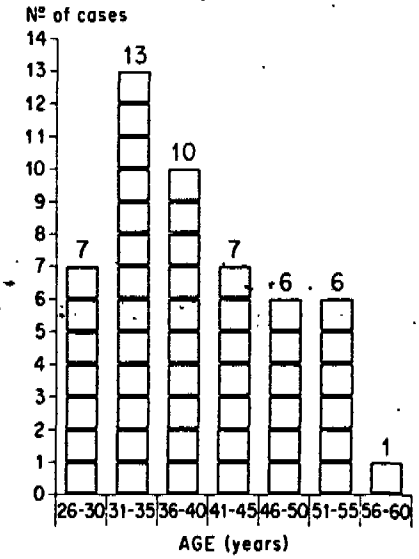

FIGURE 1. Age distribution of 50 PVC production workers (age at examination).

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TABLE 7

SYNOPSIS OF ANAMNESTIC, CLINICAL, BIOCHEMICAL, PERITONEOSCOPIC, AND HISTOLOGIC

Abbreviations used are: *Nationality:* Ger, German; Gr, Greek; Turk, Turkish; *Job Classification:* PM, VC polymerization; PC, processing of the polymer; *Peritoneoscopy:* 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; scar-like patches to broad carcinomatosis. A, augment; +, moderate; ++, m

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 (>12 (18) mU/ml)†	SGPT (>12(22) mU/ml)†	Alkaline Phosphatase	Arteriosclerosis	Raynaud-like Phenomenon	Skin Lesions	Peritoneoscopy: Surface relief	Peritoneoscopy: Capsular fibrosis
1	Ger	50	PM	21/9	—	+	+	1.5			8.7	15	15 (23)						R
2	Ger	56	PM	18/6	16–32	+	+	2	2		6.1								R
3	Ger	47	PM	18	—	+		3	5		15.6	13	19 (24)			(+)		G/Nod	R
4	Ger	46	PM	17/6	8	+	+			1.1	10.2	13(22)	15 (47)					U/G	R
5	Ger	51	PM	17	48–64			3	1.5		9.1	19	17					Nod	R
6	Ger	51	PM	16	16		+	1			11.3							G	R
7	Ger	52	PM	15/3	8	+	+	2	(2)	1.2	16.7	25	22			(+)		U	?
8	Ger	53	PM	14/6	8	+	+	1.5			5.6	15						G	R
9	Ger	44	PM	13/9	8		+	1.5				15	13					G	R
10	Ger	39	PM	13/9	16		+	3	(11)	2.0	17.6	31	23					G	R
11	Ger	48	PM	13	16–32		+		1.5		6.2	15	15					G/Nod	R
12	Ger	27	PM	12/6	—	+						13						G	P
13	Gr	40	PM	12/3	28		+			1.1			13						R
			PC	0/9															
14	Ger	52	PM	11	—	+	+	2	11	1.1	13.0	16	16					G	R
15	Ger	35	PM	9	16				3	1.1	15.1	19	17(31)				+	G	S
16	Gr	45	PM	8/6	16						8.8	13	13					U	R
17	Gr	42	PM	6/8	8	+	+	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)					G	?
19	Ger	31	PM	5/9	16		+						(28)					G	S
20	Turk	33	PM	5/9	8		+					15						G	C
21	Gr	30	PM	5	8		+				9.6	15	13						
22	Ger	34	PM	5	16	+	+		1.5		21.5	21 (21)	23 (40)		-		+		Not exa
23	Gr	36	PM	5	16		+				7.6		25						R
24	Gr	30	PM	5	8	+	+	1.5	6	1.8		90	190						R
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)					U	
27	Ger	31	PM	4/9	8	+	+	1.5			8.3	15	15						R
28	Gr	31	PM	4/0	—	++	+		6	1.7	7.1	23	25					U	S
			PC	1/0															
29	Turk	33	PM	4/0	8	++	+	6	3	1.8	25.6	25	58		-	(+)	+	G	R
30	Gr	30	PM	3/9	4	++	+	1.5			6.4	15	17						R
31	Turk	36	PM	3/9	?	+	+	1.5	1.5	2.2	22.5	25	34		++	+	++	G	?
32	Turk	33	PM	3/6	—			3			6.8	23	17		++	(+)	++		R
33	Ger	32	PM	3/6	4	+	+	6	4		12.5	19	16		++	(+)	++	U/G	S
			PC	1/0															
34	Ger	40	PM	3/6	16		+	1.5		1.1	8.6	19 (20)	15 (31)			+	+		R
35	Gr	31	PM	3/3	8–16		+				5.2	(20)						U	C
36	Gr	38	PM	3/3	8–16 (110–160)‡							13	15 (24)						C
37	Gr	47	PM	3/0	16	+	+	3			9.7								S
38	Gr	30	PM	3/0	—	+	+	3				13							C/R
39	Turk	30	PM	2/9	—			1.5			8.4	17	13						
40	Gr	33	PM	2/6	—			1	1										C/S
41	Gr	41	PM	2/3	16	+	+	1											R
42	Ger	41	PM	1/9	8		+				6.1	19 (22)	17 (47)						S
43	Gr	36	PM	1/6	8			3			6.3	17	17						R
44	Turk	33	PM	0/9	8						5.1	28	30 (23)						
			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						R
47	Gr	39	PC	5/3	16		+					(20)							R
48	Gr	45	PC	4/6	—		+				8.8	(22)	(47)						R, P
49	Gr	37	PC	4/0	44	++		6			7.0	(88)	(72)						S
50	Ger	36	PC	2/0	32	+	+	8				28 (20)	28 (38)						C

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

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LE 7

ONEOSCOPIC, AND HISTOLOGIC DATA OF 50 PVC WORKERS

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

Acroosteolysis	Raynaud-Like Phenomenon	Skin Lesions	Peritonescopy: Surface relief	Peritonescopy: Capsular fibrosis	Peritonescopy: Capsular vessels	Histology: Collagenization of sinusoidal walls	Histology: Enlargement and/or proliferation of hiltoral cells	Histology: Septal fibrosis	Spleen Size by Scintigraphy (cm)	Enlargement of Spleen	Esophageal Varices	Thrombocytopenia (<150 × 10³/mm³)
				R		(+)	+		Normal (liver scan)			+
	(+)		G/Nod	R	A/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	+	+	+
	+		C	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	+		+
			G/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	+		

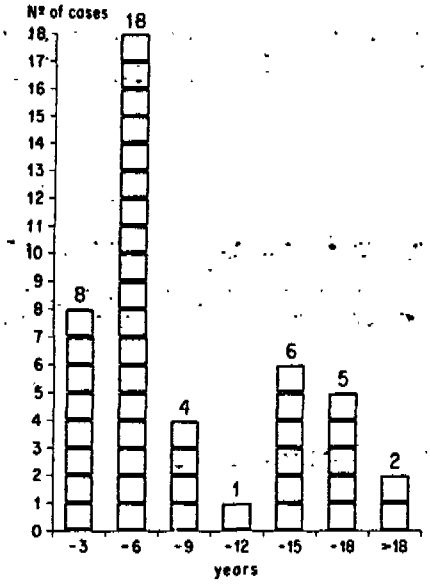

FIGURE 2. Length of exposure in 44 workers engaged in the polymerization process.

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 5 g	15
Up to 16 g	16
Up to 32 g	6
Up to 54 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 Henning* 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.

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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

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TABLE 11

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

	45-Min BSP Retention (5.0%)*	Serum Bilirubin (1.0 mg/100 ml)*	Alkaline Phosphatase† (48 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 31–60 mU/ml	13	15	20–50 mU/ml 31–60 mU/ml	12	17
	>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.[120]

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. 14) 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.[34,67,50,155] 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.[18,102] Based upon a compilation of 63,845 cases in which peritoneoscopy was performed with 48,766 guided liver biopsies, Brühl[25] 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.

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FIGURE 3. Gra
reflection), pronour
fibrosis, distinctly i
biopsy can be seen.

lower edge of
normally sharp
2. *Changes in he*
and glossy wit
sharply define
pearance due t
tion; granular
lobular archite

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

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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.[183] 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-

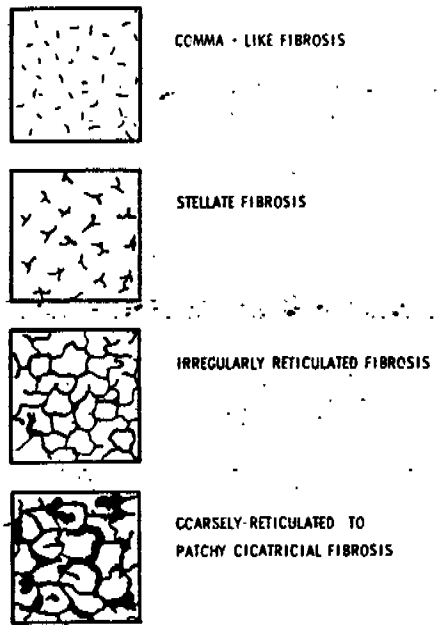

FIGURE 6. Types of capsular fibrosis of the liver observed in PVC workers.

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.)

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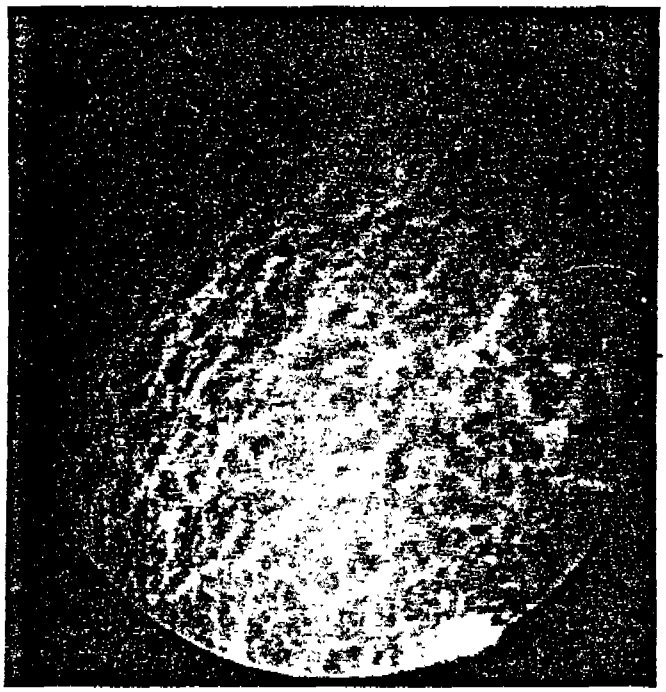

FIGURE 8. Coarsely reticular fibrosis of Glisson's capsule; right lobe. (Case no. 9; length of exposure, 13¾ years.)

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.)

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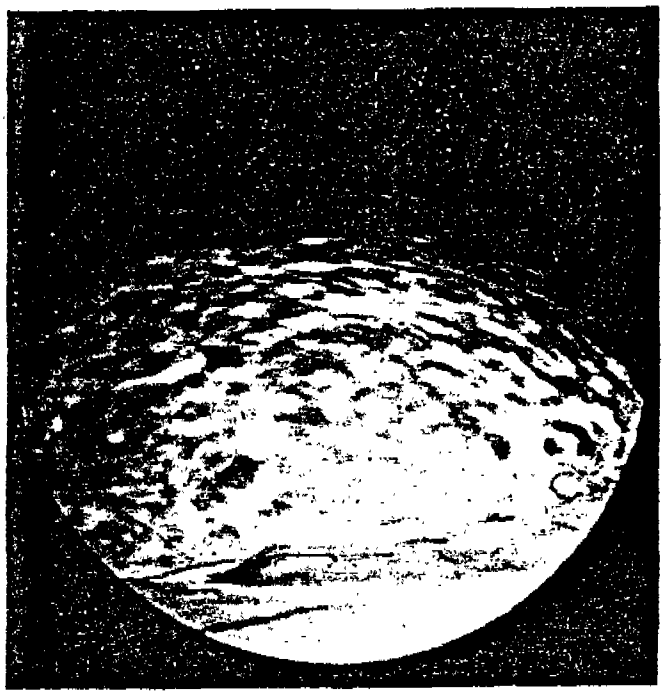

FIGURE 10. Coarsely reticulated fibrosis and patchy focal whitish capsular thickening (focal "perihepatitis cartilaginea"), resembling capsular alterations seen in thorotrastosis of the liver.[16] (Case no. 6; length of exposure, 16 years.)

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
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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).[18] 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-

HEPATOSPLENOMEGALY

	Hepatomegaly ($n = 49$)
None	31/49
Present	18/49

* In 13 cases the sp
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FIGURE 13. Degen
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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	—	—

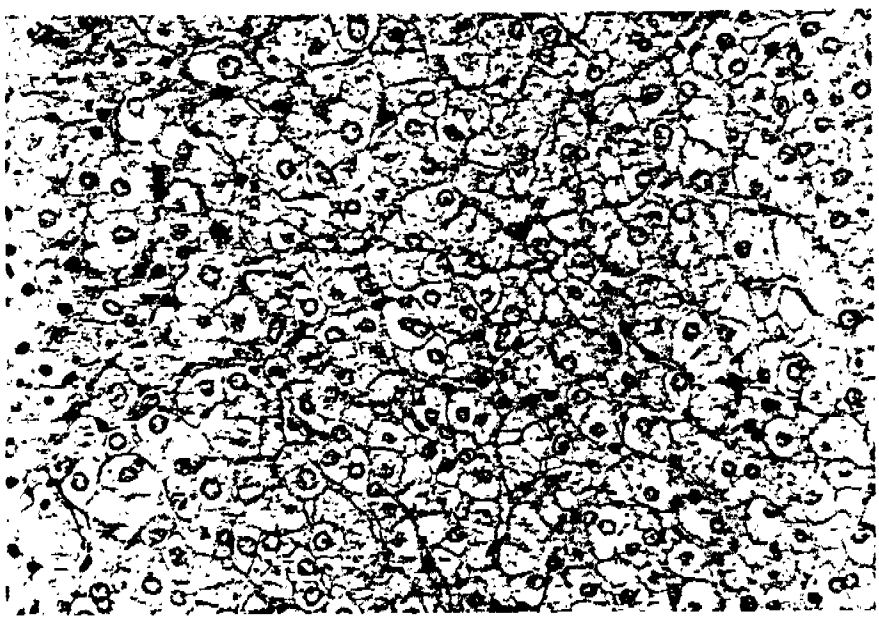

FIGURE 13. Degenerative changes of hepatocytes with hydropic swelling and granularity of cytoplasm. Occasional single cell necrosis. Note proliferation and pleomorphism of littoral cells (Case no. 14; length of exposure, 11 years; biopsy several days after last exposure). H&E (×235).

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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,[12,38,60,78,144] 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-

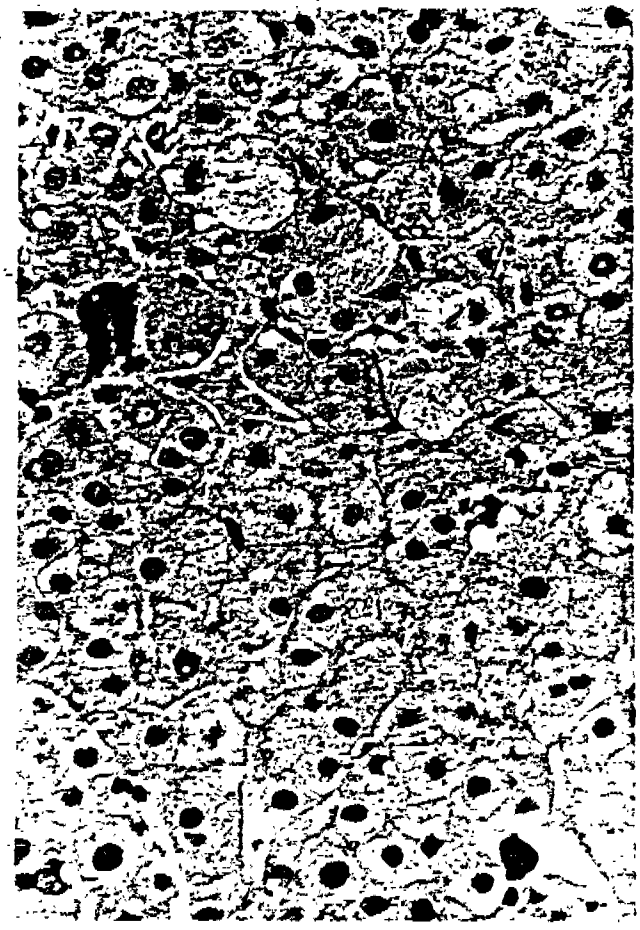

FIGURE 15. Toxic and adaptive changes of parenchyma. Conspicuous pleomorphism of littoral cells (Case no. 3; length of exposure, 18 years; biopsy 2 weeks after last exposure). H&E (×400).

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.[31,40,74]

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-

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nantly inconspicuous symptomatology (for instance, minor hepatic functional insufficiency[65,91]) 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[91] that we dealt with a symptomatology compatible with the diagnosis of chronic toxic liver damage,[72,75,76] 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[72,120,132]), *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,[60,75,79,142,156] 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.[39, 59, 162] 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,[11,15,116,117,121] or of so-called idiopathic portal hypertension,[19,67,95,102,108,110–112,149] respectively. In this disease entity, portal hypertension and splenomegaly are usually accompanied by similar alterations of hepatic surface and histology;[14,15,77,110,121,129,145,146] in some cases, however, portal hypertension seemed to have been the result of sclerosis or thrombosis of the portal vein.[19,67,95,104] 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;[14,19,95] BSP retention, however, can be readily explained by the character of the histologic lesions.[71] A certain resemblance to Banti's syndrome is suggested.[119,123] 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,[136] 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.[15, 19, 67, 77, 108–112, 118, 124, 130, 135, 148]

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.[71,108–112,120,131,138] 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[20,52,150] 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[1, 13, 17 35, 59, 66, 96, 122, 123, 134, 139, 143] 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[157]) by a toxic substance[153] may be the common denominator.

This leads back to the question of etiology.[66] 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,[21,37,60] even if one considers the unreliability of olfactory sensations[36, 83, 105, 135] and the wide range of olfactory threshold concentrations reported in the literature.[12, 21, 64, 81, 104, 106]

Except for Schumann's communication in 1934,[127] quoted by Williams[155] in 1959, very little is known about the kinetics and metabolism of vinyl chloride.[64,70,154] 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"[120]), for example, by way of "lipid peroxidation."[72,133,161] Furthermore, formation of free radicals may also be involved in the oncogenic action of vinyl chloride.[123]

Regardless of such deliberations, results of animal experiments with long-term exposure to *pure VC* have demonstrated considerable hepatosplenic injury[84,147] apart from tumorigenesis and damage to other organs.[151,152] 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[49] whether and if so how far various additives[31] or intermediate compounds[61] 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[20,62,133] during processing (e.g., calendering, moulding, extrusion, etc.) at temperatures of 100–200°C.[22, 132] At the moment, it is also open to discussion whether PVC dust, apart from damage to the respiratory tract,[22,60,103] may cause gastrointestinal symptoms,[22] for instance, by persorption.[158]

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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[20,28,61,157] and of prospective and retrospective large-scale studies[20] as well as of continuous monitoring of working areas[12,158,108,144] 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 technical 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.